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GENETICS

A Periodical Record of Investigations Bearing on Heredity and Variation

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SEX LINKAGE IN MAN[1]

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Received November 1, 1929

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INTRODUCTION

The fact that chromosomes play an extraordinarily important part in determining development is now established. Not only chromosomes, as a whole, thus function, but also their constituent genes play a specific rôle. And each such gene plays a rôle that, on the one hand, is general in the development of the organism and, on the other hand, specific for a particular morphological or chemical quality of the organism.

Each gene, we must believe, is, ordinarily, located in a particular chromosome. One of these chromosomes is found in most of the higher organisms to be to a large degree determinative of sex. It is, accordingly, called the

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sex-chromosome. A number of genes are located in the sex-chromosome and they are linked with sex itself in an interesting and curious way. In humans the female somatic cells have two sex-chromosomes (XX), one from each parental germ cell, while the male has only one X-chromosome and this is derived from the egg. It is associated with the Y-chromosome which carries few active genes.

A consequence of these relations is that sperm cells that carry an affected X-chromosome become progenitors of daughters half of whose eggs, in turn, carry the affected X-chromosome. If such eggs produce males, the males will be affected; if females, their defective X-chromosome will be balanced by a normal X-chromosome from the sperm and the females will either not show somatically or phaenotypically the defect that they carry, or will show it in a low grade of expression (see figure 1).

Now all of the sex-linked traits are linked, not with sex alone but also with each other. Accordingly we expect to find sex-linked traits associated with each other in inheritance.

It was this consideration that led the Research Committee of the AMERICAN MEDICAL ASSOCIATION to start a study of some human families with haemophilia to learn if color-blindness, or any other sex-linked trait, was in them linked with the haemophilia. Before giving our results (which were not as conclusive as hoped for) it may be well to review our knowledge of the best studied sex-linked traits in man. These are: color-blindness, haemophilia, optic nerve atrophy; also, but less extensively studied, night blindness, some cases at least of muscular atrophy, hypoplasia of white brain substance (Pelizaeus-Merzbacher disease), and some strains of myopia and of multiple sclerosis. Still other sex-linked traits have been cited, but the evidence for them is still very limited.

It is proposed to consider the best known of these sex-linked traits.

COLOR-BLINDNESS

It has been known for over a century and a quarter that some persons are defective in the color sense. Three main types of color defect are known.

(a) Achromatic vision. The central region (fovea) is alone sensitive to light. The loss of function is probably due to defective development of the cones. This condition is not known to have any hereditary factor.

(b) Red-green color-blindness; dichromatic vision. This includes the red-blind and the green-blind. Violet-blind persons have been described, but the condition is very rare. The commonest sub-type is red-blindness, called protanopia or blindness to the first essential (red) constituent of the

spectrum. Persons thus affected see the red end as an extremely low, unintense yellow. The green band also appears yellow and bright. The other sub-type includes green-blindness, called deuteronopia, or blindness to the second essential (green) constituent of the spectrum. Persons thus affected see the red end as a yellow that is only slightly reduced in intensity from normal yellow, while the green band is a yellow that is much less bright than in the case of the red-blind.

(c) Includes anomalous trichromatic vision. Persons of this type see the red, yellow and green of the spectrum; but red and green mixed in the proportions that give yellow to the normal eye do not give a good yellow to them. Two sub-groups can be distinguished here also.

Persons of one sub-group say that the mixed color is green; to make yellow more red of the spectrum must be added—this makes a yellow that is rather dull. Such persons are called "green-see-ers" or protanomals.

Persons of the other sub-group say the mixture of green and red that ordinarily gives yellow appears to them red. More green has to be added; then they see a bright yellow. They are called "red-see-ers" or deuteranomals.

The genetic problem is the relationship of these five conditions, normals, protanomals and protanops, on the one hand, and deuteranomals and deuteranops, on the other.

Before entering more deeply into the problem it is necessary to consider the statistics of color-blindness in the general population. It is commonly said that, in Europe generally, there are 4 percent of men and 0.4 percent of women affected; that is, one tenth as many women as men.

DANFORTH (1924) has argued that there is something incompatible with these proportions and the probability that the proportions of color-blind in the population are not changing. It may be said, parenthetically, that since color-blindness has been measured in large numbers of children only during the present generation we really have no basis for the conclusion that the proportion is not changing.

On the hypothesis that red-green color-blindness is due to a mutation in a gene of the sex chromosome (the X-chromosome) then the following considerations will hold. Since there is only one X-chromosome in the male, there is the same proportion of affected X-chromosomes in the male population as there is of color-blind males, namely 4 percent. Also it may be said that, for the same reason, 4 percent of the X-bearing male sperm of the entire population are defective in the gene for color discrimination that is carried in the X-chromosome. The proportion of normal to defective color genes in the male X germ-plasm is, therefore, as 96:4.

Since male zygotes derive their X-chromosomes exclusively from the egg, then in the whole population the proportion of eggs containing a defective X-chromosome is 4 percent; 96 percent have an unaffected X-chromosome.

In female zygotes there are 3 possible combinations (since each female zygote has 2 X-chromosomes). Since in all X-bearing sperm cells we have the ratio 96 percent X:4 percent X′ and in all eggs 96 percent X:4 percent X′ (where X′ refers to the X-chromosome carrying the affected gene) then in all zygotes we shall have normals 0.96×0.96 or 0.9216. Of conductors 2 times 0.96×0.04 or 0.0768. Of color blind 0.04×0.04 or 0.0016.

The above computation gives us 0.16 percent color-blind females in the population instead of the 0.4 percent alleged to occur. We see, thus, that a population consisting of 4 percent color-blind men and 0.4 percent color-blind women will produce only 0.16 percent color-blind women in the next generation, while the proportion of affected men remains at 4 percent. Thus the proportion of color-blind women to color-blind men will tend rapidly to diminish in successive generations; but if it does, the proportion of color-blind men will also diminish.

SCHIÖTZ (1922) by means of refined methods of testing for color-blindness, reaches a conclusion that 10 percent of males and 1 percent of females are color-blind. Such a pair of ratios can maintain themselves approximately in successive generations. Doubt has been cast, however, upon the reliability of SCHIÖTZ's determinations.

WAALER (1927) has examined 9000 children in the schools of Oslo using the Ishihara test as a routine test and examining by means of the Nagel anomaloscope all whose reactions to the Ishihara tests were not normal. He also examined the entire family, as far as possible, of all of the boys and the girls who had defective color discrimination.

All males proved themselves to be either normal or to belong to one of the four aberrant types: protanomal, protanops, deuteranomal, deuteranops; and, in transmission, there proceeds from each male a chromosome of a type corresponding to the condition that the male shows somatically.

The females, however, do not show somatically or phaenotypically the whole content of abnormality in the X-chromosome since they have two such chromosomes and these may be either similar or unlike. The composition of the X-chromosomes of the mother is demonstrated by the color discrimination of her sons. Also the color discrimination of her father and brothers will help with the analysis, since she receives one of her X-chromosomes from her father and one from her mother, whose constitution is in part indicated by the condition of her brother. As a result of this colossal investigation of WAALER'S it appears that the protanomal condition is

dominant over the protanops; the deuteranomal is dominant over the deuteranops; while the normal condition dominates over all. The normal, the protanomal and the protanops constitute three members in an allelomorphic series. The gene for each is located in the same point of the chromosome. Similarly, normal, deuteranomal, and deuteranops constitute an allelomorphic series located in the same gene. The author is inclined to conclude that the genes for all five conditions are identical but suffer varying amounts of kinds of damage.

WAALER's statistics indicate that 8 percent of the population of boys examined show some type of abnormality in color discrimination. One would expect 0.64 percent of the girls to show color-blindness. There are actually found 0.44 percent ± 0.07. The deviation from expectation, while considerable, is not too improbable in view of the considerable size of the probable error. The statistical findings of WAALER, therefore, show a relation between abnormal males and females that can persist in successive generations.

Anatomical basis of red-green color-blindness

A thorough critical examination of the literature, with a study of some new families, has been recently made by BELL (1926). She points out that it is uncertain upon just what modifications of the normal color discriminating apparatus color-blindness depends. Indeed, the basis of normal color discrimination is not certainly known. There is some evidence that the cones of the retina are part of the color discriminating apparatus. Thus LARSEN (1921) found that in totally color-blind persons, whose eyes he sectioned, the cones of the fovea "were short and plump where they are normally found to be long and slender." Also they had either very short outer members or these were wholly absent. There is some evidence that a central-cerebral defect is also involved, since "disturbances of cerebral origin from pathological processes may cause total color-blindness without any affection of the retinal structures." (BELL 1926, p. 172).

Inheritance of red-green color-blindness

Color-blindness is commonly considered to be due to a recessive gene mutation located in the sex chromosome.

If the father is color-blind, his sole X-chromosome carries the defective gene. If the mother is color-blind, both of the two X-chromosomes, by hypothesis, carry the defective gene. But a mother may carry the defective gene in one of her X-chromosomes, while the other is unaffected. Such a mother, called a conductor, will be phaenotypically normal.

While all the eggs carry an X-chromosome, only half of the sperm cells do (the other half carrying the Y-chromosome which plays a small rôle in inheritance). The sons get their single X-chromosome from the egg only; so if the mother is without gametic defect none of the sons will be color-blind even if the father is. The daughters get an X-chromosome each from the egg and sperm. If the X-chromosomes of the egg are all without the gene defect, then the daughters can distinguish colors even if the sperm cell brings in a gene-defect in its X-chromosome. In the latter case, the heterozygous daughter can pass on the defective X-chromosome to half of her offspring. In the case of the sons half will be color-blind; in the case of the daughters half will be conductors—forming some eggs containing the defective X-chromosome.

Do the heterozygous females always have normal color discrimination? BELL (1896, p. 195) cites one sibship containing three color-blind females, the father of whom has been definitely tested by NETTLESHIP (1912) and pronounced to have normal color vision; and in several unquestionable cases color-blind women have been demonstrated to have some sons with normal color vision. In BELL's (1926, p. 233) pedigree (chart 418, II 4), a woman, aged 54, was thoroughly tested by wools, Nagel's cards and the Stilling test and found to be definitely color-blind; she required the help of others in choosing her dresses. She had a number of daughters and 7 sons. Three of these sons are clearly color-blind. Of the 4 others 3 were tested for color-blindness. The first was tested by Sir J. H. PARSONS, who found him normal with Holmgren's wools, Stilling test and colored lights. The other 2 boys were given an equally rigid test and showed fine color discrimination. Of the 4 daughters tested all were found normal. The condition of color vision of the parents of the affected mother is not definitely known. On the chromosome theory of heredity, it seems most probable that (unless the father was color-blind) the mother was heterozygous for color discrimination, and that the normal gene is imperfectly dominant. Thus we conclude that heterozygous females sometimes lack perfect color discrimination.

In figure 440 of BELL'S work (1926, p. 238) the "mother" (VI 13) is color-blind and has a color-blind father and a carrier mother; and at least 2 of her 3 sons are color-blind. Except that *all* sons should be color-blind, this accords with expectation, since in the "mother" both X-chromosomes are probably affected.

A summary of cases given by BELL is instructive. When both parents are color-blind all (4) sons and (5) daughters are color-blind. When the father is affected and the mother's stock is so likewise, 49 percent of sons

and 37 percent of daughters are affected. When both parents are normal and the mother's stock is affected 61 percent of the sons and 2 percent of the daughters are affected. Even when the mother is affected and the father normal only 3 percent of the daughters are affected. There is no doubt that color-blind fathers have carrier daughters who, in turn, have color-blind sons. That is, the defective chromosome passing through the (heterozygous) daughter is transmitted to half of her sons, who thus lack capacity for color discrimination.

HAEMOPHILIA

Normally the blood flows in well circumscribed, walled spaces in the body—the blood vessels; if the walls of the vessels are cut blood has the property of making a temporary wall, or plug, by clotting.

The irregularities in the physical behavior of blood are due (1) to weaknesses, or abnormalities, of the vessel walls, permitting extravasation into the tissues; (2) to abnormalities of the clotting process or (3) to a combination of the two preceding.

The first and third classes of cases are recognized by the symptom of purplish spots arising in the skin in consequence of such extraversation of blood. The commonest types are known as purpuras, or purple spot diseases.

Of the purpuras, the first type is characterized by the tendency to form purple specks which flow together to form larger patches—usually on the legs and arms and often symmetrically. In extreme cases violent intestinal and gastric symptoms—pain and vomiting—occur. The patient usually recovers in a few days. The symptoms are accounted for on the ground that bodily toxins cause paralysis of capillaries, or larger vessels; so that tone and resistance to pressure are lost. Probably the loss of tone is due to a preceding intoxication of the spinal innervation of these finer blood-vessels. There is no evidence of an hereditary tendency.

In the other type of purpura and in the so-called haemophilia, there is an abnormality in the blood which interferes with normal clotting, so that the clotting or coagulation time is greatly delayed or clotting wholly inhibited. (*For the determination of coagulation-time.* There are several methods in use, such as those of VIERORDT, W. SCHULTZ, BÜRKER, MORAWITZ and BIERICH, WÖHLISCH, SAHLI-TONIO, KOLLMANN and others. The salt-plasm method of WOOLRIDGE and NOLF is highly spoken of by BAAR and STRANSKY (1928). It is applied as follows: The blood flowing from the vein of the arm is received into an equal quantity of 10 percent NaCl solution (2 marks on the test tube) and smartly centrifuged. There results

a salt-plasma that does not spontaneously coagulate. To test coagulation, 1 cc of this salt-plasma is diluted with 4 cc of distilled water in a test tube that has been well cleaned with alcohol and ether and dried. One drop of egg yolk is added. Every 5 minutes one observes whether or not the plasma is coagulated, by gentle inclination of the test tube. It is desirable always to make 2 parallel determinations and 2 controls with normal blood. Normal salt-plasma coagulates within half an hour; haemophilic blood often remains uncoagulated or shows after many hours to some days an often incomplete coagulation.)

Clotting is due to the formation of threads of fibrin in the blood plasma which entangle the corpuscles and form a plug. This is an invaluable property in preventing bleeding to death at wounds; but it is a dangerous property if it occurs inside of blood vessels, since the plug might well enter into and close up essential vessels, causing perhaps instant death. Fibrin is formed, however, only in the air; and by an interaction between a substance in the blood plasma and a substance in some of the cellular elements of the blood, particularly the blood platelets, which rapidly disintegrate in the presence of air. The substance in the plasma is called fibrinogen and the enzyme from the cells is called thrombin. It is the interaction of the two that produces fibrin.

Just as fibrin is formed only out of the blood plasma in the air, so thrombin is formed in the cells, but only in the presence of calcium. The calcium is necessary to the activation of the thrombin. Blood collected in a vessel containing a weak solution (a little over 0.1 percent) sodium oxalate will not clot; but if a saturated solution of sodium chloride be added it clots at once. It is believed that the calcium is necessary to the formation of the thrombin out of something in the cell—and this something HOWELL calls prothrombin or "thrombinogen." It is also called, by BORDET, (1920) zytozym.

It is HOWELL'S (1913) hypothesis that the prothrombin of the blood is ordinarily prevented from forming thrombin by a substance that he calls anti-thrombin. But in the air, cellular elements, or the plates in the blood, neutralize the action of the anti-thrombin and, in the presence of calcium, enable the prothrombin to form thrombin.

In the second type of purpura, sometimes called purpura haemorrhagica, or thrombopenic purpura, there occur spontaneous bleedings in skin (forming purple patches); at mucous membranes—nose, gums, etc.; and internal organs—such as kidney and retina. Usually there is no bleeding at joints as in haemophilia. An histological study of such blood indicates that the number of blood plates is much reduced—so that

thrombin can not be formed in normal amount. It is on this account that this disease is sometimes called thrombopenic purpura.

An hereditary history for this disease has been given in a number of cases, which indicate perhaps a dominant heredity. Possibly in one or more of the genes of an autosome there is a positive something that prevents the formation of blood plates in normal amount and thrombin-forming function.

In *haemophilia* the symptoms are:

(1) After a cut, a persistent hemorrhage occurs that is scarcely controllable by artificial means. From the smallest wound the blood may trickle for days and weeks.

(2) Spontaneous hemorrhages appear, especially, persistent nose bleed; also striking effusions into the joints, which become enlarged and blackened—"blood joints," or "bleeder joints."

Probably only males are affected and most affected males (60 percent) die before the age of 8 years. In the 11 percent that attain the age of 22 years, the symptoms are ameliorated and after about 40 they are never severe.

The degree of symptoms is variable and in respect to symptoms biotypes appear in various families.

Cause of haemophilia

BAAR and STRANSKY (1928) after examining the results of all experimental work on the subject conclude:

Neither the fibrogen content of the haemophilic blood, nor the thrombin content of the haemophilic serum is diminished. No increase of coagulation-inhibiting factors is found.

The disturbance of coagulation in haemophilia is thus to be sought in the first phase of thrombin formation.

Although there are divergent experimental results, BAAR postulates as most probable, an insufficiency of a cell enzyme (prothrombin of HOWELL or zytozym of BORDET) and its retarded relinquishment by the blood plates.

From this point of view there is a gene in the X-chromosome that determines the production of a normal amount (and kind) of zytozym (prothrombin) in the cells and especially cellular elements of the blood. In haemophilia this gene is modified—and in different degrees—resulting in biotypes of haemophilia of varying degrees of defect.

Two rules of inheritance have been suggested.

NASSE's rule: Only males are affected; the disease is transmitted through unaffected daughters to their sons.

LOSSEN's rule. No affected male has direct male descendants who are affected. The transmission is only from female to female or female to male; never from a male to his daughters.

It should be easy, one would think, to decide between the rules of NASSE and LOSSEN by examination of the pedigree charts that have been published. But such examination leads to much disappointment. Of the 235 pedigree charts published in the work of BULLOCK and FILDES (1911) the only ones that show grandchildren of a certainly affected male are: Nos. 373 (TENNA family), 382, 387, 389, 402, 408, 424, 426, 431, 436, 445, 462, 465, 468, 474, (478), 490, 493 bis, 512, 528, 535, 540, 541, 548, 562, 570, 581, 584. But No. (478) is regarded as a valueless pedigree by BULLOCK and FILDES. In the 27 significant pedigrees there are 31 affected males who have grandchildren. Together these 31 males have 47 daughters that have children. Together these daughters have 128 sons, and of these $78\pm$ are affected. Thus there are $78\pm$ haemophilic grandsons of affected males descended in the female line from affected grandfathers. Certainly this result is opposed to LOSSEN's rule: "Nur Männer sind Bluter, vererben aber, wenn sie Frauen aus gesunden Familie heiraten, die Bluteranlage nicht." Of the 31 affected male progenitors of grandchildren there were only 3 who did not have affected grandsons. It is quite impossible to believe that of these 31 men 28 (or 90 percent) married wives belonging to haemophilic families. On the other hand there are some statistical irregularities in the pedigrees. Expectation is that one-half of the sons of "conductor" mothers will be haemophilics. Of 128 sons recorded, $78\pm$ (some uncertainties) are regarded as bleeders. This is 14 more than expectation. Also, of these "conductor" mothers the daughters who have any haemophilic sons should have them in the proportion of 50 percent of all sons. Actually of 45 recorded 34 are given as bleeders. These deviations from expectation are too great to be due merely to insufficient numbers. It seems probable that a larger proportion of haemophilic sons than of normal sons is recorded. The recorder of the pedigrees has his attention focussed on bleeders in the family, he records all such; but he is less careful to inquire into and record non-bleeders.

It seems the most probable conclusion that haemophilia follows the usual course of sex-linked inheritance, which is stated in NASSE's rule.

An important inquiry is: Where are the haemophilic females? Such are to be expected from certain matings, just as color-blind females arise from certain matings. Although bleeding females have been described, careful

analysis usually shows that they are either women affected with purpura or else they are very incomplete cases of true bleeding appearing in "con-

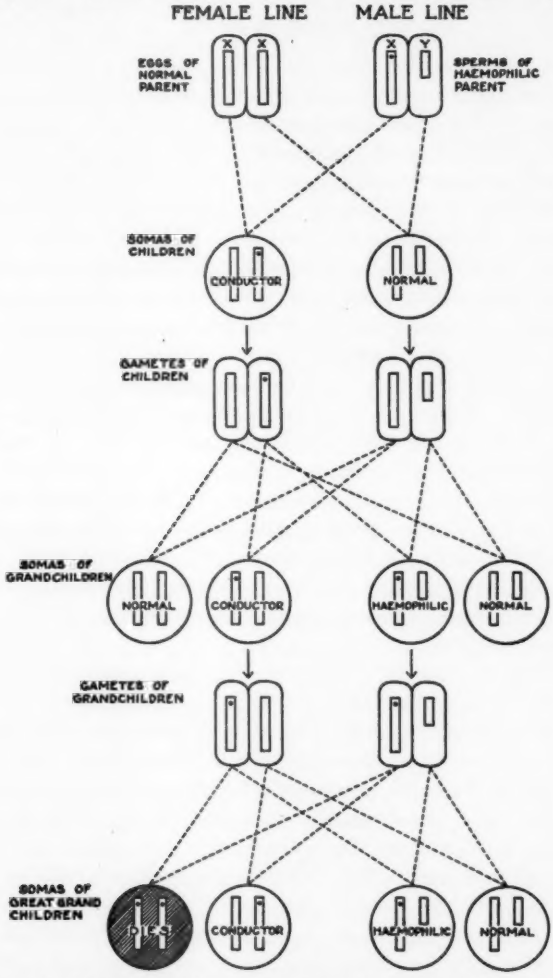

FIGURE 1.—Scheme of inheritance along male and female lines of the gene for haemophilia. Drawing by Miss M. B. CHAMBERS.

ductors" (that is heterozygous females). The most reasonable explanation of the absence of typical haemophilic symptoms in the female is that the

zygote that receives 2 affected X-chromosomes dies early, usually before birth (figure 1).

Hereditary Optic Nerve Atrophy (Leber's disease)

This disease commonly begins at adolescence with a loss of clear vision, due to the development of an area of partial, or total, blindness (scotoma) in the axis of vision. Just because this area is that of greatest color discrimination, color vision is greatly reduced. On ophthalmoscopic examination the disk of the optic nerve is found to be grayish or whitish instead of pink. In later stages the margins of the disk become ill defined; also the blood vessels of the retina become narrowed and more tortuous.

Hereditary opticus atrophy belongs to a genus of diseases that is characterized by degeneration of the optic nerve. In the genus are also (1) intoxication nerve atrophy, also called "neuritis axialis chronica sive actua," and (2) diabetic nerve atrophy.

Intoxication nerve atrophy appears subsequent to excessive use of alcohol or tobacco. Wood alcohol blindness belongs in this category. After abstinence vision is improved. In the hereditary form no improvement follows abstinence (though abuse of narcotics often precedes its onset). Also the narcotic type is often one-sided, while the hereditary type is bilateral—though vision may be affected in one eye earlier than the other. Moreover in the narcotic form the sexes are nearly equally affected; while in the hereditary type females are not usually affected. Also in the narcotic type onset is ordinarily slower and occurs later in life, and vision is less often completely impaired.

The diabetic species of optic nerve atrophy is associated with a high percentage of blood sugar and affects the sexes equally.

The specific diagnosis of hereditary opticus atrophy is based on the inability to control it by abstinence from narcotics, or on its non-association with high blood sugar, on a relatively early and sudden onset (usually under 28 or even 25 years) and on a prevailing tendency to affect several males in the same family and, much more rarely, females. Thus in a number of affected fraternities, of 537 sons who grew up 390, or 72.6 percent, were known to be affected; whereas in 428 matured daughters of the same fraternities only 32 daughters, or 7.5 percent, were affected (table 1). Of the affected, 92 percent were thus males and 8 percent females. Again Wilbrand and Saenger (1913) found in 308 affected cases 272 males and 36 females, or 88 and 12 percent respectively. The population of persons affected with opticus atrophy is divided into males and females roughly in the proportion of 9 to 1.

The diminution of vision usually proceeds farther in the case of opticus atrophy than in the case of narcotic amblyopia, so that fingers can not be counted at a greater distance than 3 meters. In narcotic amblyopia vision is usually reduced one-half. But the best diagnostic criteria of Leber's disease is its hereditary quality.

Incidentally it may be mentioned that biotypes of hereditary opticus atrophy seem to occur. Some biotypes are characterized by early onset (at 8 or 10 years); others by prevailingly late onset (35 to 50 years). Some biotypes are characterized by cessation of degeneration at an early stage—with persistence of slight amblyopia; others by practically complete blindness. Apparently there are biotypes in which the heterozygous female tends to show opticus atrophy. The existence of the biotypes reminds one of allelomorphic series, of which the more nearly normal representatives are dominant over the more defective.

The enormous predominance of males early led to the conclusion that Leber's disease is a sex-linked one.

In typical sex linkage the percentage of incidence of the female sex is equal to the square of the incidence of the male sex. The reason for this is that while X′ indicates the incidence of the single affected sex chromosome that causes the sex-linked trait in (1X) males, X′X′ indicates the percentage incidence of two affected X′-chromosomes necessary to the production of 2X-females who show the sex-linked trait. Nobody has computed precisely the proportion of mature males in the native male population who have optic atrophy. Assume it as .005, or 5 per thousand of the population, then the proportion of females would be 25 per million. In other words the affected females would be 1/200th as common as affected males. The tables that I have collected contain about 75 affected females and 481 affected males. However, not all of these females have been seen. FLEISCHER and JOSENHAUS found in the literature only 6 cases of females that had been directly investigated. But KAWAKAMI (1926, p. 576) has the opinion that in Japan the incidence of females is much higher than in the European cases considered by FLEISCHER and JOSENHAUS. In any case, in the selected families affected females are about 1/10th instead of 1/200th as numerous as males. This result may be due to the expression of the trait in many heterozygous females.

Let us now consider the incidence of affected males and females following given matings in which affected X-chromosomes are probably involved.

The question has been frequently raised whether optic nerve atrophy follows the law of NASSE, like color-blindness; or the law of LOSSEN,

according to which an affected man has no affected descendants in first, second, or later generations (unless intermarriage occurs with females of affected stock).

Tables 2a to 2e contain data drawn from the pedigrees given for families whose defect is most probably true Leber's disease. In selection of families use was primarily made of the critical examination of DREXEL (1922). To DREXEL'S accepted cases are added certain earlier ones not considered by him and a number of families that have been published since his work. KAWAKAMI (1926) has published pedigree charts for a lot of cases that had appeared in the Japanese literature and had been overlooked. These I have not included. Most of them are fragmentary and, in general, the incidence of affected females is so high that they constitute a class quite different from the European and North American cases. I have, however, included KAWAKAMI'S own case. One wonders whether the Japanese physicians have a somewhat different criterion of Leber's disease from the European or whether the factor, or factors, that make for hereditary opticus atrophy lie in different chromosomes in the peoples of the two continents.

Considering this tabulation it appears that in pedigrees where 50 percent of affected males are expected (the mother being a conductor) 63 percent and 66 percent are found in matings I and IV respectively. The unexpectedly large proportion of affected males may be due to a selection of data: namely, of just the affected brothers, the others being unreported. In the type of mating (II) where the mother is affected and therefore 100 percent affected males are expected—73 percent are found. This result might be interpreted to indicate that some of the affected mothers are only heterozygous.

In matings (I) where the father is normal and the mother a conductor, no affected daughters are expected, but 6 percent are found, clearly indicating that some heterozygous daughters are affected, even though atypically. Where the father is normal and the mother is affected (mating II) the proportion of affected daughters rises to 17 percent. In mating III (affected father, genotypically normal mother) 2.8 percent of the daughters are affected. These results are irregular. They suggest that either there are biotypes in which the heterozygous female is affected; or else a special accessory factor for blindness exists in some strains.

In mating III, where the father is alone affected, there are very few sons affected. In the 2 matings that yield affected sons the mothers are really unknown. Though they were almost certainly not affected they may readily have been conductors. In GINSBERG'S family an affected man had

3 sons by one woman and 1 by another, all affected. We know nothing about these women though they were probably not affected. For all we know to the contrary they may have been sisters and both conductors. In the other families, comprising together 81 grown sons, none are affected. In view of our ignorance of the mothers the results of mating III are not opposed to NASSE's law.

Again, KAWAKAMI (1926, pp. 592–594) has tabulated the best known families with optic nerve atrophy, with special reference to the vision of the mother's father of an affected person. There are 56 such mother's fathers described and 47 not described. Only 4 are known to have been blind. KAWAKAMI contrasts this condition of not more than 7 percent with the 40 percent occurrence of known color-blind mother's fathers in color-blind families. This difference is the more striking since the proportion of known to actually atrophically blind is doubtless greater than the proportion of known to actually color-blind. The 4 cases of maternal grandfathers affected with optic atrophy may well be due to inheritance from the mother's mother as a conductor. The fact of much higher incidence of affected maternal grandfathers in color-blind families than in families with optic nerve atrophy is strong evidence that inheritance does not follow the same law in both cases.

MACKLIN (1927), despite this evidence, or perhaps without fully considering it, is inclined to doubt the validity of LOSSEN's law in opticus atrophy. She points out that usually too few generations are known or there are no male descendants of daughters of the affected man. This criticism is all too true. Still there is a remarkable absence of daughters of men with opticus atrophy who are certainly conductors. Referring to mating III, we find that in the family of USHER (1927) of 3 daughter's children of the blind grandfather not one was affected, although apparently of the age of incidence. Again in the family of HIRSCH (1923) the 3 sons of 2 daughters of an affected man (II 1) are unaffected; and again the married daughter of blind III 8 had 3 grown sons of whom none was affected. Also, of 5 other married daughters none of the 3 sons was affected.

Out of the hundreds of grandchildren of men with opticus atrophy the only sure cases of daughters' sons with opticus atrophy that I have been able to find in the literature (not explicable by the female lines) are the following:

In GOULD's (1893) case, in the first generation there is a man with opticus atrophy one of whose daughters (II 4) had 4 sons who survived to maturity and one of these (III 9, who died at 40) had opticus atrophy (figure 2).

In HANCOCK's (1908) case a man (I 1) who had opticus atrophy had a normal daughter (II 1) whose 3 sons (III 1, 5, 8) all had opticus atrophy. She had a daughter also (III 3) who had 4 sons of whom 1 had opticus atrophy. A sister (III 7) of the last mentioned daughter's daughter had 2 affected sons. II 1 had another daughter, III 2, and her daughter (IV 3) had an affected son V 2(figure 3).

These two families offer remarkable exceptions that only enforce the general rule that in typical Leber's disease affected males have no affected descendants. On the chromosome theory of inheritance, as indeed applied by KAWAKAMI (1926, p. 590), the union of a Y-chromosome with the

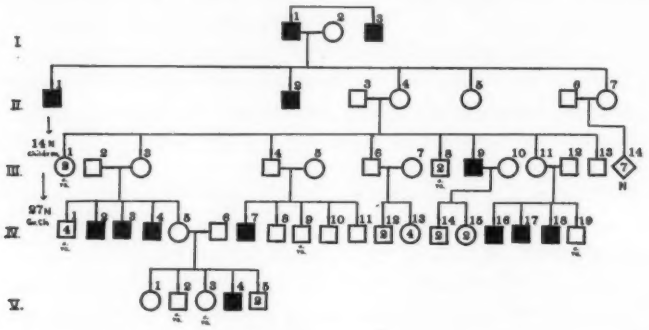

FIGURE 2.—Pedigree of opticus atrophy, by GOULD, 1893. II 1, age at onset unknown; became blind from same type of disease which has since appeared in the later generations. His father was blind and deaf somewhat late in life. I 3 affected at 28 years, like his brother. II 1 affected, died at 86. II 2 affected at 28. II 4 eyes weak and watering; but not blind, died at 62 years. II 5, horned in eye by a cow; blind before 40. II 7 became blind late in life, cause unknown (probably cataract); no affected children. The later generations follow the rule of sex-linked inheritance; except that IV 7 offers difficulties since his sex chromosome was derived from his mother who, apparently, does not belong to the family with opticus atrophy.

affected X-chromosome from a female conductor permits, indeed, the optic nerve atrophy to develop in the male. But somewhere in the development of the zygote or of its sex cells, or during maturation the affected X-chromosome becomes either modified or lost. Or it may be that the sperm cells that carry the affected X-chromosome do not function. At any rate, in the vast majority of cases the affected X-chromosome that has been associated with the Y-chromosome does not function again. Of course, if daughters of affected males produce no conductor-daughters; or such daughters produce few, or no, sons the same result would follow. In the families of GOULD and

of HANCOCK considered above the Y-chromosome does not experience its usual, but peculiar, fate.

Finally, there are a few families in which inheritance of optic nerve atrophy appears to follow a non-sex-linked and nearly, or perfectly, a dominant type of inheritance. The case of KNAPP (1904) is an example. Here an affected father has 2 affected sons out of 5; and 2 affected daughters out of 3. One of the affected daughters marries her normal cousin and they have 4 affected sons out of 5 and 1 unaffected daughter.

Again, WAARDENBURG (1924) tells of a family in which the grandfather, who was examined ophthalmoscopically, showed optic nerve atrophy. His daughter (also observed ophthalmoscopically) had a similar loss of

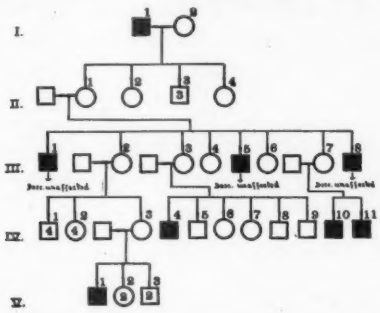

FIGURE 3.—Pedigree of opticus atrophy, by HANCOCK, 1908. I 1 in third decade sight failed; later improved; lived to be 100 years old. III 1 vision failed in both eyes at between 20 and 30 years; never recovered, a heavy smoker. III 5 lost vision like III 1; after a year recovered sight; no abuse of alcohol or tobacco. III 8 attacked at between 20 and 30 years; not abstemious; no recovery. III 1 had 4 sons and 3 daughters, and he had 5 grandsons, none affected at the time of report.

vision. By a normal man she has 5 sons, 3 affected; and 5 daughters, 1 affected. This looks like a case of a dominant gene (instead of a recessive) located in an autosome (instead of X-chromosome). Genetically it is as different from ordinary Leber's disease as can well be.

KROPP (1927) described a family in which the father began to lose vision at 21 years, having a partial opticus atrophy on both sides. His wife, so far as all tests go, has normal vision. They had 5 children. The first son and first daughter had normal vision. The second daughter had a neuritis back of the eyeball of unexplained etiology, and on both sides a central scotom. The third daughter had atrophic optic nerves, with relative central color scotom, on both sides. In this case the genetic condition is like that in WAARDENBURG'S case cited in the last paragraph.

WAARDENBURG (1924, Stammbaum IV, V) gives two pedigrees where the marriage of unaffected first cousins has resulted in affected sons and daughters. These pedigrees suggest that the gene concerned is a recessive, autosomal one.

These aberrant cases are quite confusing. That a recessive, sex-linked gene might come to lie in an autosome is quite possible. A similar exchange of genes between non-homologous chromosomes has been described in Datura (BELLING and BLAKESLEE 1926), and elsewhere. That a gene responsible for continued functional vigor should in some cases by "weakness" (recessiveness) produce opticus atrophy and in other cases by "strength" (dominance) produce likewise the same type of opticus atrophy seems incredible. Possibly just a delicate median balance of functional activity of this gene is required for normal functioning of the optic nerve.

The conclusion of this analysis of the cases of Leber's disease is that it is generally a recessive, sex-linked trait with a usual failure to reappear in descendants of affected males. However, it is expressed occasionally in females who are "conductors" or heterozygous for the trait. Moreover, the trait of hereditary opticus atrophy is sometimes induced by a gene that is not located in the sex-chromosome.

OTHER SEX-LINKED TRAITS

Brief mention may be made of other sex-linked traits. No attempt is made here to analyze them or to extend the bibliography.

Hypoplasia of white brain substance, as worked out by MERZBACHER (1909), seems to be a case of sex-linkage, but so far confined to one family.

Night blindness, or hemerolopia of the sex-linked type, occurs in which males only are affected. This is not to assert that females can not be affected—the available pedigrees are very few in number. BELL (1922) lists only the great CUNIER-TRUC-NETTLESHIP pedigree, that of NETTLESHIP and MORTON and 29 minor ones. The large CUNIER-TRUC-NETTLESHIP pedigree of the NOUGARET family of VENDÉMIAN includes both males and females. There are 12 families in which the males only are affected. AMMANN'S (1898) case is typical, with 14 affected males and no affected female. All affected males inherit through unaffected females. Incidentally, all affected males are said to be myopic, but this is based only on family tradition.

Myopia, or short sightedness, in some families, runs a sex-linked type of inheritance. Thus, in some of the night-blind families with affected males only there is also myopia in some (or all) of the affected males. Even without night blindness some families have been described, like

those of WORTH (1906) (see figure 4) and OSWALD (1911), in which males alone are myopic and inherit through unaffected females.

A sex-linked inheritance of megalocornia has been described by KAYSER (1914).

Pseudo-hypertrophic muscular paralysis of GOWERS (1879) is also sometimes sex-linked. In sex-linked families about 6 times as many males are affected as females. TSCHERNING (1921) has discussed inheritance in this disease.

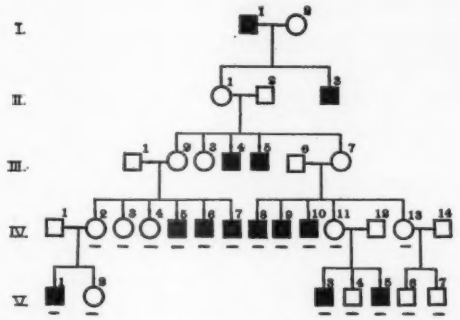

FIGURE 4.—Pedigree of family with hereditary sex-linked myopia (WORTH 1906). The black symbols indicate myopia. The underscored symbols represent persons examined. In addition some members of the IIId generation were seen. The other cases are classified on the basis of statements of relatives. The myopia was measured as 10 or 12 D, with some astigmatism.

Other traits for which sex-linkage, in certain strains, has been found are: coloboma, nystagmus, microphthalmia, ichthyosis, webbed toes, toothlessness, deficiency in sense of smell and wanderlust, or nomadism.

SOME NEW PEDIGREES OF HAEMOPHILIA

During the summer of 1927, under a grant from the Research Committee of the AMERICAN MEDICAL ASSOCIATION, Mr. C. V. GREEN undertook to trace families with haemophilia in order: (1) to check on them the method of inheritance and (2) to learn if in any of these families there was also color-blindness. The special purpose of the investigation was to find evidence of sex-linkage of these two characters.

Mr. GREEN took preliminary instruction in the determination of haemophilia from Professor W. H. HOWELL, to whom we desire to express our gratitude. For determination of color-blindness the Stilling Isochromatic plates were used. Mr. GREEN's itinerary took him to Dushore, Athens, Sayre and Wilkesbarre, Pennsylvania (July 12–15), to Findlay and Day-

ton, Ohio (July 18th and 19th), to Rushmore, Minn. (July 25), to Sibley, Iowa (July 26), to Frederickton and Des Moines, Iowa (July 28–August 1), to Williamsport, Pennsylvania (August 15), to Cleveland, Ohio (August 30, 31) and to Detroit (September 2). A considerable amount of time was spent on trips that yielded no result, owing to the removal of families.

R-family (figure 5)

The most extensive series of families included certain descendants of the well-known MOLYNEUX strain of Pennsylvania. A MOLYNEUX daughter married a distant cousin of the same MOLYNEUX stock and by him had 4 sons, half with haemophilia (II 3, 5) and 2 daughters (II 7, 8). A sister of the husband mentioned in the last sentence had 1 son (II 9), a bleeder.

II 3 lives in Wilkesbarre. At about 10 years of age he cut his finger badly and it was then first discovered that he was haemophilic. He has

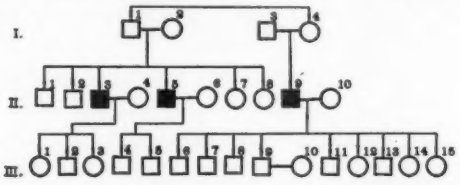

FIGURE 5.—R. family with haemophilia. The black squares indicate bleeders.

been twice given up to die by physicians, as a result of bleeding from extracted teeth. He has not been troubled lately as he takes very good care of himself (own statement). He was given the Stilling test and proved to have a very good color discrimination, much better than his wife's. One of their sons was given the Stilling test and did exceptionally well in it.

II 5 (brother of II 3) works at Athens, Pa. He has been in the hospital at Sayre on two or three occasions from hemorrhages, one of which was caused by a rather severe bruise on the shin. Blood collected until a large black lining was formed. When this was lanced a severe attack of bleeding followed. II 5 did only fairly well on the Stilling test; but quite as well as II 3's wife.

II 9 (cousin of the foregoing) is a well informed farmer, living near Dushore, Pennsylvania. He appreciates the method of inheritance of haemophilia. His worst attack of bleeding resulted from an infected finger, followed by "blood poisoning." On this occasion he nearly bled to death. His teeth are in bad condition but he hesitates to have them extracted,

fearing the probable consequences. He did fairly well on the Stilling test; better than his wife. Three of their 9 children, who were tested, did well.

The distribution of haemophilia in this family accords with the law of sex-linked inheritance of haemophilia; a typical sex-linkage confined to the male sex. None of the offspring of affected males are affected. Presumably the consorts of the affected males are genetically normal. There is no color-blindness in this family.

M-family

This is also a branch of the MOLYNEUX family, I 2 having been a MOLYNEUX before marriage. She had 7 sons. Of these 2 are known to have been haemophilic. II 8 was seen. He is affected by slight shaving cuts no more than is a normal person. His worst attack occurred about a year ago when he had his teeth extracted. At that time he was confined in a hospital at Sayre, Pennsylvania for a considerable period. It was feared that the hemorrhages would be fatal.

The color discrimination of II 8 is good, as good as that of his wife. Also the color discrimination of his daughter III 1 and son III 2 in each case is good—about the same as in the mother; the 9 year old sister made 2 more errors than her 7 year old brother.

P-family

The propositus, I 1, is a member of the MOLYNEUX family and lives in Detroit, Michigan. He is a pale, sickly man. His teeth are in very bad condition but he does not dare to have them extracted. He is troubled much with rheumatism. The slightest bruise causes swellings at the joints, especially at the knees and elbows, which are distended almost constantly. A slight cut on his hands causes a great amount of bleeding. When he was a child his mother had to watch at his bedside day and night for six weeks, as a result of having a milk tooth extracted. As a child he had an arm broken which could not be set right because of the excessive bleeding. According to his sister his whole life has been ruined on account of his defect. His case is the most severe of any seen among the MOLYNEUX. His color discrimination was not tested.

A-family

In this family, also one of the MOLYNEUX strain, the wife, I 2, is a sister of I 1 of the P. family. She married an unrelated man. They have 2 sons, ages 20 and 9 years respectively, and a daughter, aged 7. The second son, II 2, has haemophilia. He was first discovered to be a bleeder

when about 5 years of age. He had a deciduous tooth extracted and there was profuse bleeding for 9 or 10 days; a serum was successfully used to stop it. Bleeding at the mouth has several times occurred, especially around the teeth; and his pillow is sometimes badly stained with blood, or he has to leave school on account of bleeding at the mouth. Cuts on other parts of the body do not trouble him greatly. He bleeds from them hardly more than a normal person. He is not yet, at 9 years, troubled with swellings at the joints.

None of the family were color-blind. The largest number (about 13) of errors (Stilling test) was made by the 7 year old girl.

Gross family

The pedigree of this family is given in figure 6. It is the family to which most attention was paid. It is the only one in which color-blindness was certainly combined with haemophilia.

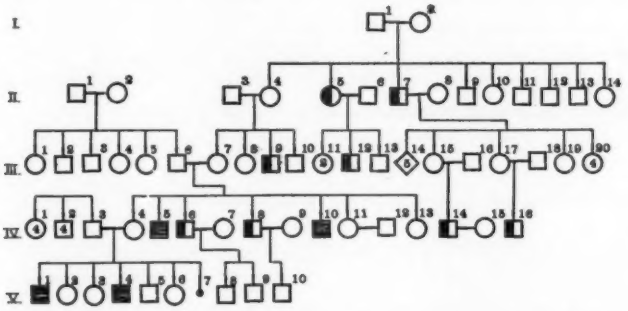

FIGURE 6.—Pedigree chartof the GROSS family in which both haemophilia and color-blindness occur. Color-blindness is indicated by the half-black symbol and haemophilia by the horizontal stripes. It will be noted that haemophilia is not found back of generation IV, while color-blindness occurs in generations II, III and IV. The two conditions are not combined in any one person.

III 7, the mother of the color-blind and haemophilic fraternity, stated that the haemophilic members of this family have always been recognized as such when only a few months old, in this respect differing from the MOLYNEUX family. Later they acquire painful swellings at the joints, originating even from only a very slight bruise.

III 7 has had 7 children, 4 boys and 3 girls. None of the girls were affected somatically, though the eldest has had 2 affected sons out of 3. Of III 7's children, IV 5 died in infancy from bleeding from a cut in the mouth made by a piece of glass.

IV 6 shows no symptoms of haemophilia. He was tested for color discrimination and was found to be color-blind.

IV 8 also shows no symptoms of haemophilia and is also color-blind. Thus both failed completely on the Stilling test group 2; also groups 4, 5, 6, 7 and 8, except that II 6 got 3 figures right out of 16, in the group 6 test. They made such errors on the group 9 test as to lead to the suspicion that they carried diminished susceptibility to red.

These two persons are the only ones in the immediate family, so far as studied, who showed color-blindness. In their mother's family color-blind persons (male only) occur as follows: Her brother, III 9; her aunt, II 5 (doubtful); this aunt's son, III 12; aunt's brother, II 7; and 2 of his daughters' sons, IV 13, IV 15.

There are no cases of color-blindness on the father's side of the house. Accordingly we may conclude that the gene for color-blindness was carried in the X-chromosome—as that is derived by sons from their mother's side only.

In the main fraternity there is one other male, brother of the color-blind men, who has haemophilia. IV 10, DANIEL G., is 28 years old, and had a bad spell about 3 months previously. These attacks resemble rheumatism, and have followed bad sprains of which he was, at the time, unaware. At other times he can do heavy work and not be troubled. ALFRED V 1 is the same way. When DANIEL was in the army hospital he had his ear pricked and it bled so profusely that his shirt became covered with blood. This came as a surprise to the physicians who a short time previously found that a finger prick was not followed by excessive bleeding.

In the fifth generation are two children, V 1 and V 4 who have a history of bleeding. V 4 died recently from pneumonia and bleeding. V 1, at 19 years, is tall and anemic. At the time of Mr. GREEN'S visit in August, 1927, he was just recovering from a strain of some kind and had been laid up for 3 or 4 weeks. All of the other children look healthy.

Color tests were applied to the mother (IV 4) of the fraternity described in the last paragraph. She made only a few errors until she came to group IX, 2. In this group of 4 characters she attempted only 1, and this was correct. She made only 1 error with group IX, 1 and one error in group X, 1 and 2. She apparently has a trace of blue-green blindness.

Color tests were applied to the four oldest members of the fraternity of the haemophilic boy (V 1). He himself has remarkably good color discrimination, much better than his mother's. He made only one error in reading the 30 plates. V 2 ♀ made only one slight error. V 3 ♀ made only the same single error that her sister did. V 5 ♂, apparently about 6 years

old, made 14 errors. Especially did he fail in group IX—the test for blue-yellow. As this age may be too early for entire color discrimination capacity to be functional one can not conclude that any of the children are color-blind.

B-family

This is a branch of the MOLYNEUX family, the connection being through I 2, who was evidently a conductor. She had 10 children, 6 sons and 4 daughters. Four of the sons had haemophilia. Of these sons II 8 alone survives at the age of 70 years. He seems well preserved and looks normal, He was about 10 years old when it was first discovered that he was a bleeder. Later he had a permanent tooth pulled and it bled so badly that his pillow would be soaked in blood. Cuts and bruises sometimes trouble him. From a bad bruise on the shin he was confined to bed for 3 or 4 weeks. With the Stilling plates his color discrimination appeared normal.

II 8 has had 5 daughters and 1 son, all without haemophilia. Two full sisters of II 8 have respectively 1 son out of 2 and 1 out of 3 who are haemophilic.

III 2, daughter of II 8, has 3 sons, all haemophilic and 1 daughter. She herself has no bleeding tendency. She made 8 errors in the Stilling plates, all in miscalling a 3 an 8.

All of her sons are, as stated, badly affected with bleeding. One of them plays football and his bruises are terrible to see. Cuts cause all of these boys trouble. IV 5 was seen. He is a fine, normal appearing boy, tall and large for his age. His color discrimination is good.

G-O family

This is a branch of the MOLYNEUX family. I 2 was a PARDOE, allied to that family. She has a son who has haemophilia; also a daughter, aged about 12 years.

III 1, R.G., at 23 years is well conditioned but somewhat pale. He has had 3 bad attacks of haemophilia: (1) At 10 years he bumped his forehead. After seeming to heal, the wound, on the ninth day, broke out again. He was confined to his bed on this occasion. (2) At about 15 years he cut his foot on glass. After the blood flow was staunched it broke out again after a week, or 10 days; but he did not have to go to bed on account of it. (3) About 2 months before the interview he had a lower molar pulled. He was laid up for about 2 weeks. Treatment with horse serum worked satisfactorily. The young man has often had to stop nose bleed by the

use of a calcium compound, perhaps calcium lactate. He has good color discrimination, as shown by use of the Stilling test.

Pol family

This is a Ukrainian family, living in Cleveland, Ohio. The father, I 1, is dead; the mother, I 2, is about 25 years old. She is not a bleeder and can not find, after inquiry, any other cases of bleeding in the family. She has good color discrimination, confusing only 3's for 8's.

Her eldest son is 10 years old; and looks pale. He has had 4 bad periods of bleeding and has been in the hospital for them. At the time of Mr. GREEN'S visit he was in the hospital due to a cut under the tongue from a piece of iron. A vesicle of blood under the tongue, size of a bean, was cauterized and removed. He had 4 transfusions of blood from his mother during about 2 weeks, the amount of transfusion being about 100 to 300cc; and the infusion was temporarily successful. The boy was recovering.

By Stilling's plates the mother read all figures correctly except for calling five 3's eights. The son, NICHOLAS, could not read the figures of group IX. Also most of the figures at group VI, especially 1 and 4, could not be read. The sister, aged 9, made a few errors which may be due to her immaturity. It seems probable that NICHOLAS carries 2 sex-linked defects; haemophilia and color-blindness.

Car family

In this Cleveland family the mother was interviewed by telephone through Doctor C. W. WYCKOFF'S cooperation. This mother, who is herself free from haemophilia, has 2 living sons and had 2 others who died in early infancy. The family has been traced back for 5 generations and no case of haemophilia found previously. The elder son was discovered to be a bleeder at 6 months. He has been repeatedly troubled with bleeding and has had 5 blood transfusions; clotting time before transfusion 9 minutes, after transfusion 6 minutes. There are swellings at the joints and blood extraversations; but the lad seems to be getting better. The younger son was also a bleeder. If he bit his tongue or lip, the hemorrhage would persist for days. Clotting time 9–1/2 minutes.

Nor family

This Cleveland family was not seen but the haemophilic son of about 6 years was known by Professor T. WINGATE TODD of the Department of Anatomy, WESTERN RESERVE UNIVERSITY and Doctor DAVIS of the CITY HOSPITAL to be haemophilic.

Nar family

This Cleveland family was visited by Mr. GREEN. The father (H.S.N.) says he bleeds badly—though not so much of late. The worst time he had was when his teeth were extracted, for there was great difficulty in stopping the flow of blood. Of the mother's family little is known.

There is a daughter, MARGARET, aged 8 years. When she was a baby she was diagnosed by Doctor T. B. SMITH as a case of haemophilia. She has never had swellings at the joints. Doctor C. W. WYCKOFF finds her blood-coagulation time to be 15 minutes, and the coagulation is then not typical. A tonsil operation having been decided on she was given calcium lactate, 10 grains 3 times a day for 1 month prior to the operation. Her coagulation time was reduced to 5 minutes. Despite every precaution in the way of ligation of vessels the operator had a great deal of trouble for 10 or 12 hours in controlling the hemorrhage.

There are 2 sons, aged 4 and 2 years. It is early to say whether or not they are haemophiles. Doctor WYCKOFF states that they bleed very easily and for a long time after minor injuries, but their joints do not show swellings or blood extraversations. No color tests were made on this family.

CROSSING OVER IN MAN

Since there are several known sex-linked characters in man it is natural to look for crossing over. Crossing over in the children might be found in cases where a female with at least two sex-linked genes was mated with the "normal" male. These conditions are not easy to meet, since sex-linked phaenotypic traits are relatively uncommon in females. But the conductor female can be inferred from her relationship to affected males. It is possible that crossing over might be found when the male carries 2 sex-linked genes. But in view of the relative inactivity of the Y-chromosome in man, as in Drosophila, it is to be expected that in the human, as in Drosophila, there may be no crossing over in the male.

In Mr. GREEN'S study an attempt was made to find a person, either man or woman, who bore two genes for recessive, sex-linked traits. Haemophilia and color-blindness seemed the most promising. The GROSS family, indeed, showed both traits—in males only. But in this family no individual showed both traits. In the GROSS pedigree, III 7 is the sister of a color-blind man and her mother has a color-blind brother and the mother's sister has a color-blind son. This incidence of color-blindness in near relatives supports the conclusion from her progeny that she carries the color-blindness in one X-chromosome. III 7 transmits haemophilia to half of her sons and, accordingly, we conclude that she carries the gene

for haemophilia in one X-chromosome. The X-chromosome carrying color-blindness and the X-chromosome carrying haemophilia are apparently not the same X-chromosome. One might hastily suppose that if III 7 got the X-chromosome with the color-blind gene from her mother's side, she got that carrying the gene for haemophilia from the father's side. But, if so, the father would be haemophilic. But SIMON GROSS (II 6), her father, was seen and there is no doubt that he is free from the bleeding tendency, for his blood clotted in 1 minute. (GRACE ALLEN: E.R.O,. A 8102–25).

Accordingly we are forced to the conclusion that both genes for color-blindness and haemophilia are carried in the X-chromosome that the mother (III 7) received from her mother or else that this X-chromosome underwent mutation in the haemophilic gene in III 7. Had the haemo-

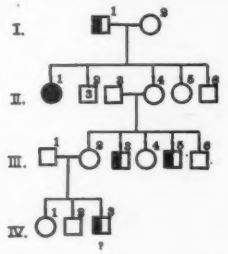

FIGURE 7.—Pedigree chart of a family with haemophilia combined with color-blindness (MADLENER 1928). I 1 both haemophilic and color-blind. II 1 (his daughter) is haemophilic III 3, 5 both haemophilic and color-blind. IV 3, certainly haemophilic and possibly color-blind.

philic gene been in the X-chromosome that III 7 received from her mother and which carried the color-blind gene we might expect haemophilia in III 7's brothers or her sister's sons, or those of her mother's sisters. III 7 had 2 brothers neither of whom was a haemophilic while 1 was color-blind. III 7 had 1 sister whose 2 sons were normal. III 7's mother had a color-blind brother but no haemophilic brother, out of 5 brothers. One sister had 2 sons, 1 color-blind. The other sister had 1 daughter who had 2 sons, not affected, and 3 daughters 1 of whom had 9 sons unaffected. The pedigree suggests that the haemophilia mutation had occurred in the paternal X-chromosome, while in the ovary of III 7.

The possibility that 2 sex-linked traits occur in the same individual has actually been realized in the remarkable German pedigree recently published by MADLENER (1928) which starts with one, H. DÖRR (figure 7). He (I 2) was a haemophilic and also color-blind. He had 7 children, of

whom 1 son was haemophilic and 1 daughter a conductor (to her 2 sons) of both haemophilia and color-blindness. In this case the sex-chromosomes of the mother of the 2 affected sons carried both a gene for haemophilia and one for color-blindness. Also a daughter of this mother certainly carried the gene for haemophilia and perhaps that of color-blindness (her 4 year old son is haemophilic but a little too young to be sure of his inability to distinguish colors). In this family, then, the linkage of 2 sex-chromosome genes is clear. Since the number of offspring is small it is not significant one way or the other that there is no evidence of "crossing over."

The pedigrees of AMMANN (1898) and of PFLÜGER (1881) published by BELL (1922) show no crossing over between night blindness add myopia and in the case of NETTLESHIP (BELL'S figures 319–320 and 323) the incidence of these two traits is irregular. The cases of PAGENSTECHER (BELL, figure 318) and CUTLER (figure 325) are too fragmentary to permit of any conclusion as to the rate of crossing over.

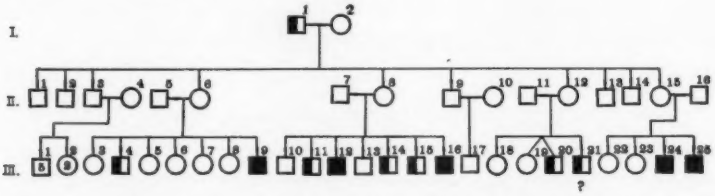

FIGURE 8.—Pedigree chart of a family combining night blindness and myopia (NEWMAN 1913). I 1 probably night blind and myopic. All symbols that are wholly black indicate night blindness without myopia; symbols that are half black indicate night blindness combined with myopia. There is doubt whether or not III 21 is myopic.

Instructive in the matter of crossing over is the pedigree given by NEWMAN (1913) and reproduced, in part, in figure 8. The significant individuals are described as follows:

I 1 at report 74 years old, night blind from infancy, "short sighted" (probably myopic). His six sons and four daughters are all normal. Of these children II 3 is not night blind or myopic and none of his 7 children are affected. II 6 is unaffected but is a conductor since both of her sons are night blind. III 4 "was unmistakably night blind and showed the usual associated defects" which the "Treasury of Human Inheritance" interprets as showing myopia. We have followed the "Treasury" in this interpretation. Thus the grandson had both the sex-linked traits of his grandfather. III 9 is typically night blind at 4 years. His sister, a university student of zoology, writes: "Brother can not see anything out of the light at night except that on bright nights he can see anything between

him and the sky." (Windmill, trees, houses, etc.) "He could not distinguish his express wagon, his kitten or other objects on the ground." "He is not short-sighted at all." In this case, then, only one of the two sex-linked defects was received by the night-blind son.

II 8 (Mrs. UZZELL) had 7 sons, III 10–16. III 10 is normal. III 11 is night blind, myopic and strabismic. III 12, at 13 years, is "night blind, without any other optic defect." Here again one of the sex-linked traits is lost. III 13 is normal. III 14 at 8 years is night blind, myopic and strabismic. III 15 at 6 years is likewise night blind, myopic and strabismic. III 16, at 4 years is night blind, but without other associated defects.

II 12 (Mrs. E. F. FLOYD) has had 2 sons, both night blind and 2 daughters normal. III 20, at 5 years, is clearly myopic and strabismic. The evidence is less clear that he is night blind.

III 21, now dead, "lived long enough to exhibit sure signs of night blindness. No facts about associated defects."

II 15 ♀ had 2 daughters and 2 sons. III 24, aged 4, is "night blind, but without other defects." III 25, aged 8 months at time of report, "shows unmistakable signs of night blindness, but no other defect." These two cases would seem too young for a critical statement.

To sum up, III 12, at 13 "night blind but without any other optic defect," a first cousin of the intelligent, trained reporter, is one clear case of inheritance of one of two genes linked in the mother's father. III 9, III 16 and III 24 are night blind but still too young for it to be certain that they are myopic. No case of myopia without night blindness occurs in this fraternity. However, the chance of failure to get just this condition is considerable.

That such a segregation of myopia from night blindness is possible is indicated in pedigree No. 325 of the "Treasury." In the latest generation of a night blind family one of 4 brothers shows night blindness and myopia. His eldest brother at 28 years had myopia of 9 D, but no night blindness. Their mother had 2 brothers. Of these 1 died at 9 years, night blind, but nothing is said about refraction. The other brother seen at 46 years was night-blind. His vision was poor but myopia is not mentioned. As the mother has a myopic (and night blind) nephew it seems highly probable that she carries both defects in one of her X-chromosomes and that crossing over has occured in the gamete that went to form the eldest son.

We may conclude from these still incomplete facts and considerations that there is good evidence of crossing over in sex-linked characters of man. There is then in this phenomenon also no distinction between the genus Homo, Drosophila among insects and some flowering plants.

DISCUSSION

A review of sex-linked characters in man yields something of a surprise that in a species whose traits have been so long analyzed as man's there should be so few clear-cut sex-linked characters known. In Drosophila perhaps a hundred sex-linked characters have been determined. To be sure, there are only 4 pairs of chromosomes in Drosophila where there are 24 in man but even this fact does not account for the difference.

Another genetic difference between man and the insect is that while in the latter the sex-linked characters are mostly simple and clean-cut most of the sex-linked characters in man are so complex that their genetic behavior is not obvious. Red-green color-blindness alone seems fairly simple. Haemophilia is lethal when duplex and optic nerve atrophy, even if we eliminate the obviously non-genetic forms, shows many irregularities, such as the usual failure to reappear in the sons of daughters of affected men.

An interpretation of the confusing nature of sex-linked inheritance in man is to be sought, I conclude, in the same causes that are responsible for the generally small number of simple clean-cut genetic traits in man. Eye color and albinism, defects of eyes and appendages and Huntington's chorea among nervous diseases are the genetically simplest traits. Most traits, like pigmentation of skin and hair, aberrant proportions of body, and other bodily defects, mental traits of most sorts, and the susceptibility to many diseases, have a very complex genetic basis.

In general, it appears that man, perhaps just because he lies at the end of the most highly differentiated of evolutionary lines, has accumulated more mutations than any other species. Mutations have been added to preexisting mutations of the same organ. Also, it is probable that through translocations the same gene has been transferred, perhaps repeatedly, from one chromosome to another so that a gene is sex-linked in some strains and not in others. And, possibly through new relations to other genes, a trait that is recessive (or unexpressed in the heterozygote) in one strain becomes dominant (expressed in the heterozygote) in another. All of these possible complications have to be kept in mind in the study of human heredity. Probably in no other species is inheritance so complicated. This is not to suggest that the search for the inheritance factors in human traits has to be abandoned, but rather it has to be undertaken on a larger scale, with a greater expenditure of effort and funds. The importance to humanity of an understanding of the origin and development of human traits is so great, the issues at stake are so tremendous, that

research on a broader basis is urgently called for and would be wholly justified in its results.

NEED OF A REPOSITORY OF FAMILY HISTORIES

The study of sex-linked traits brings home very vividly to the geneticist the many difficulties in the study of human genetics. One of these is the time elapsing between the human generations. If the observer is a young man, of say 30 years, he may hope to observe the young children of a family, their parents and one or more grandparents, also collaterals. Such a young observer may, under fortunate conditions, see these children grow to maturity as he himself progresses toward old age. He may, before he dies, observe these children's children. Thus, under the most favorable conditions, he can see two complete mature generations; one incomplete one (of the grandparents) and one of immature individuals. For the study of inheritance of some characters this may suffice; but these favorable conditions are, alas, rarely realized. The observer wishes that, for his research, he had the contemporary physical and medical records of an earlier generation. But if any of them ever existed they have probably been destroyed. Then he regrets that there is no depository of medical and performance records about people (as there is about race horses and cows).

In the case of sex-linked traits, where a generation is regularly skipped, and 2 or more may be, this need is especially acute. An example will illustrate this need. Suppose we have observed opticus atrophy in a young man of 20 years, and we desire to know if it be of the hereditary type or not. The parents, now 40 to 60 years of age, are not affected. Of the grandparents probably half are dead and any medical records about them have probably been destroyed. We must rely upon the testimony of the "parents" and their siblings, if any, as to the condition of sight in the grandparents, use of narcotics, diabetic symptoms, etc. The record we get from the parents will often be very incomplete. Were medical records extant, how eagerly would they be examined!

Or the case may be that of two parents both affected with opticus atrophy. At the time of observation they have children of 10 to 2 years. How important to know the history of these children 10 or 15 years later! Yet the observing physician may in the meantime have moved or the family may have found a home elsewhere and there is no one to follow up the family and record the subsequent history of the children. Were there a depository, in which the full record with names and addresses might be preserved, then the early history would not be lost and a student of hereditary opticus atrophy might complete the medical history of the family

and draw important biological conclusions. It ought to be regarded as against the public interest to destroy medical records. Individual interests are, of course, to be considered and safeguarded; but the interest of the race should be regarded as supreme.

SUMMARY

The different sex-linked traits show differences in genetic behavior. Red-green color-blindness behaves like a typical sex-linked trait. Haemophilia is exceptional in that all duplex recessive female zygotes die. Optic nerve atrophy appears in several genetic types, only one of which is typically sex-linked, and in that type daughters of affected males rarely have affected sons. Female conductors form a genetic stolon from which affected males bud off. Also the incidence of opticus atrophy in females is unexpectedly high, probably due to the expression of the trait in the heterozygous condition.

Other sex-linked traits that are rare or less carefully analyzed are: hypoplasia of brain substance (MERZBACHER), night blindness (or hemeralopia), some strains of myopia, pseudohypertrophic muscular paralysis of GOWERS, and megalocornia. To these traits wanderlust or nomadism may be added. Still less well documented are coloboma, nystagmus, microphthalmia, ichthyosis, webbed toes, toothlessness and deficiency in sense of smell.

Since two sex-linked characters occurring in the same family should show linkage in inheritance such "double-recessives" were looked for. In a haemophilic family (GROSS) color-blindness was found, but the haemophilia appeared to be of such recent origin that linkage of its gene with that of color-blindness could not be studied. A family containing double recessive individuals (DÖRR) has been described. It is probable that the concurrence in some families of night blindness and myopia is due to sex-linkage. Crossing over between the genes of night blindness and myopia appears in the family described by NEWMAN, and more irregularly in a few others.

Finally the need of a repository of family histories to provide, in time, documentary evidence of traits of members of earlier generations—especially important in sex-linked traits—is stressed.

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TABLE 1

Incidence of hereditary optic atrophy in the offspring of various types of matings. N, normal; Con, conductor (heterozygous) female; Atrp, phaenotypically with opticus atrophy.

MATING		SONS				DAUGHTERS			
		Number		Percent affected		Number		Percent affected	
FATHER	MOTHER	Total less †'d	Affected	found	*expected*	Total less †'d	affected	found	*expected*
1 N	Con.	419	263	63	*50*	328	26	8.9	*0*
2 N	Atrp	26	19	73	*100*	24	4	17	*0*
3 Atrp	N	86	5	5.8	*0*	72	2	2.8	*0*
4 Atrp	Con.	3	2	66	*50*	1	0	0	*50*
5 Atrp	Atrp	3	1	33	*100*	3*	0	0	*100*
		537	390	72.6		428	32	7.5	

* These daughters are still young!

† Died young.

TABLE 2a

Incidence of hereditary opticus atrophy in progeny of specified matings. Mating I. F, Normal; M, conductor.

REFERENCES	Reference to Mother	SONS				DAUGHTERS				CONDUCTORS		Remarks
		No.	X or †♀♀	Affected No.	Affected Percent	No	X or †♀♀	Affected No.	Affected Percent	No.	Percent of fertile females	
LEBER (1871) 1 fam.	I 3	5		5	100	1	0	1	100	..	..	a
LEBER (1811)+VOSSIUS (1900)+MÜGGE (1911). See DREXEL, 1922, p. 25.												
LEBER'S IV fam.	II 2	4		4	100	2	..	0	0	..	..	
PUPALL (1876)	I 2	3		3	100	3	..	0	0			b
SCHLÜTER (1883)	I 2	1		1	100	2	.	0	0	1	50	
	I 3	3		3	100	1		0	0	1	100	
	II 2	1		1	100	1	1	..	..			
	II 4	1		1	100			..	..			
	II 8	2		2	100	1	1	..	..			
SCHLÜTER (1883)	I 1	3		2	67	1		1	100			c
	I 3	2		2	100	?						
LAWFORD (1887)	I 1	2		2	100	1		1	100			d
	I 2	3		3	100	4		0	0			
HASWELL (1888)	I 2	2		2	100	2		2	100			
	III 7	1		1	100	7		0	0			
BROWNE (1888)		3		3	100	2		0	0			e
SOMYA (1892)	I 1					2		0	0	2	100	
	II 1	2		2	100	0		..	..	..	..	
	II 2	3		2	67	1		1	100	..	..	
	II 1	0		..	..	3		0	0	1	33	
	III 2	6		4	67	5		0	0	..	..	
DESPAGNET (1892)	I 2	4		4	100	1		1	100	..	..	f
GOULD (1893)	III 3	5		1	20	5	2	0	0	2	67	
	IV 3	7	4	3	100	1	0	0	0	1	100	
	IV 8	4	1	3	100	0						
	V 6	4	1	1	33	1	0	0	0	..	..	

TABLE 2a (*continued*)

REFERENCES	SONS					DAUGHTERS				CONDUCTORS		Remarks
	Reference to Mother	No.	X or two	Affected		No.	X or two	Affected		No.	Percent of fertile females	
				No.	Percent			No.	Percent			
GOULD II (1893)	I 2	3	0	2	67	2	0	0	0	..	..	
WESTHOFF (1895)	I 2	2	0	2	100	1	0	0	0	1	100	
	II 2	3	0	3	100	1	0	0	0	1	100	
	III 2	5		4	80	1	0	0	0	..	..	
SNELL (1897)	II 2	4	2	2	100	5	0	0	0	..	..	g
LEITNER (1897)	I 1	3	0	3	100	1	0	0	0	1	100	
	II 4	4	0	3	75							
LEITNER (1898)	I 2	3	0	0	0	9		0	0	3	33	
	II 1	3		3	100	3		0	0	..	..	
	II 2	4		1	25	3		0	0	..	..	
LEITNER (1898)	II 5	2		1	50	7		0	0	..	..	
POSEY (1898)	II 7	2		1	50	3		0	0	1	33	
	III 3	1		1	100							h
RAYMOND (1898)	I 2	1		1	100	1		0	0	1	100	
	II 1	3		1	33	2		0	0	2	100	
	III 1	2		1	50	1		0	0	..	..	
	II 2	1		1	100	..		..	..	..	..	
	I 2	0		..	..	3		..	..	3	100	
	II 1	1		1	100	1		0	0	0	0	
	II 2	4		2	50	1		0	0	..	..	
	II 3	2		1	50							
HAWKES, (ERO) (1900 I)	I 2	4	2	2	100	1		0	0	1	100	
	II 5	4		3	75	5		0	0	1	20	
	III 3	2		2	100	3		1	33			
HAWKES (1901 II)	I 2	2		2	100	1		0	0	1	100	
	II 2	4		4	100	1		0	0	1	100	
	III 2	2		2	100	0		..	..	..	..	
HEINSBERGER II	I 2	3		2	67	1		0	0	..	..	

TABLE 2a (*continued*)

REFERENCES	Reference to Mother	SONS				DAUGHTERS				CONDUCTORS		Remarks
		No.	X or tw	Affected		No.	X or tw	Affected		No.	Percent of fertile females	
				No.	Percent			No.	Percent			
LAEBER 1902-GUZMAN 1913	III 2	8	4	4	50	6	2	2	50	1	1	i
BRAMWELL (1903)	I 2	3		1	33	2		0	0	2	100	
	II 2	3		1	33	2		0	0	..	..	
	II 3	2		1	50	5		0	0			
KOWALEWSKI (1906)	II 2	3		2	67	1		1	100			j
USHER (1906)	II 3	8		3	38	3		3	0			
	III 7	3		2	67							
CONTO (1907)	I 1	3		2	67	1		0	0	1	100	
	I 3	2		1	50							
	II 3	1		1	100	1		0	0			
HANCOCK (1908)	II 1	3		3	100	5		0	0	5	100	
	II 6	3		1	33	1		0	0	..	..	
	III 2	4		0	0	5		0	0	1	20	
	IV 1	1		1	100	0		..	..	..	..	
	III 3	4		1	25	2		0	0	..	..	
	III 4	3		3	100	4		0	0	0	0	
NETTLESHIP (1909, IV)	I 1	6		4	67	2		0	0	1	50	
	II 7	1		1	100	2		0	0	..	..	
(1909, VI)	I 4	4		2	50	1		0	0	..	..	
(1909, VII)	I 2	6		4	67	2	1	0	0	..	..	
EVANS (1909)	I 3	6	2	3	75	3	1	0	0	1	50	
	II 9	4	1	1	25	0		0	0	..	..	
BACH (1909)	III 4	1	0	1	100	0						
RAYMOND & KÖNIG (1909)	II 1	3	0	1	33	2		0	0	2	100	
	III 1	2	0	1	50	1		0	0	..	..	
	III 2	1	0	1	100	0		..	..	..	..	
MUGGE (1911, II)		3		2	67	0		..	..	..	..	k
LUTZ (1911)	III 2	5		3	60							
	II 7	2	1	1	100	2	1	0	0	..	..	
	II 3	2		2	100	2		0	..	1	50	

TABLE 2a (*continued*)

REFERENCES		SONS				DAUGHTERS				CONDUCTORS		
	Reference to Mother	No.	X or †vv	Affected No.	Affected Percent	No.	X or †vv	Affected No.	Affected Percent	No.	Percent of fertile females	Remarks
TAYLOR & HOLMAN (1913 II)	0	3		1	33	4	1	0	0	2	67	
	I 2	6		4	67	4				0	0	
	I 5	3		3	100	4				1	33	
HENSON (1917 II)	I 1	2		1	50	3	0	0	0	2	67	
	II 3	0				2	0	0	0	2	100	
	II 5	0		..	..	4				2	50	
	III 1	2		0	100	0	0	0	0	..	..	
	III 2	3		1	33	0	0	..	..	..	..	
	III 7	2		1	50	3	0	0	0	..	..	
	III 9	2		1	50	1	0	0	0	..	..	
FLEISCHER & JOSENHAUS (1920)	I 2	2		1	50	3	0	0	0	3	100	
	II 3	4		0	0	2	0	0	0	1	50	
	II 4	3		2	67	3	0	0	0	2	67	
	III 4	2		2	100	4	0	0	0	3	75	
	III 10	3		0	0	3	0	0	0	1	25	
	III 15	3		2	67	2	0	0	0	1	50	
	IV 1	6		3	50	1	0	0	0	..	..	
	IV 2	5		2	40	6	0	0	0	..	..	
	IV 3	1		1	100	1	0	0	0	..	..	
	IV 16	4		2	50	0	..	..	..	..		
	IV 21	1		0	0	1	0	0	0	..	..	
	IV 27	5		1	20	3	0	0	0	..	..	
DULEUTRA (1920) ERO	II 7	3		2	67	2	0	0	0	..	..	
MORLET, (1921) ERO	I 2	7	1	5	84	4	0	0	0	3	75	
	II 2	6	2	3	75	6	1	1	20	..	..	
	II 4	1	0	1	100	4	0	0	0	..	..	
	II 9	6	?	2	33	1	0	0	0	..	..	

TABLE 2a (*continued*)

REFERENCES	Reference to Mother	SONS				DAUGHTERS				CONDUCTORS		Remarks
		No.	X or †vg	affected		No.	X or †vg	Affected		No.	Percent of fertile females	
				No.	Percent			No.	Percent			
VOGT & (KNÜSEL) 1922	II 1	2	0	2	100							
	II 2	3	1	2	67	4	1	0	0	3	100	
	III 7	4	1	1	33	6	1	0	0	..	..	
GINZBURG (1923)	II 8	2		1	50	2		2	100	..	..	1
HIRSCH (1923)	III 11	2		2	100	3		0	0	3	100	
	IV 25	2		1	50	1		0	0			
	IV 28	1		1	100	2		0	0	..	..	
WORTON (1913)	II 1	4		2	50	4		0	0	1	25	
	II 2	2		1	50	3		0	0	1	33	
	III 2	7		3	43	1		0	0	0	0	
WAARDENBURG (1924)	II 1	2		1	50	3		0	0	3	100	
	III 1	3		2	67	3	1	0	0	0	0	
	III 2	3		2	67	4		1	25	4	100	
	III 4	5		2	40	3		0	0	3	100	
	IV 7	3		1	33	0		0	0			
	IV 8	1		1	100	1		0	0			
	IV 9	1		1	100	1		0	0			
	IV 16	4		2	50	4		1	25	..	..	
	IV 20	2		1	50	0		..		..	..	
	IV 23	6		1	17	1		0	0	..	..	
MEYER-RIEMSLOH (1925)	IV 4	3	2	1	100	9	2	1	14	6	100	
	V 4	3		3	100	3		0	0	2	67	
	V 9	0	..	..	..	2	..	0	0	2	100	
	V 12	1		0	0	2		0	0	1	50	
	VI 4	3		2	67	3		0	0	2	67	
	VI 15	1		1	100	1		0	0	1	100	
	VI 16	1		1	100	0		..	..	..	..	
	VI 17	3		3	100	0		0	0			

TABLE 2a (*continued*)

REFERENCES	Reference to Mother	SONS				DAUGHTERS				CONDUCTORS		
		No.	X or †♀	Affected		No	X or †♀	Affected		No.	Percent of fertile females	Remarks
				No.	Percent			No.	Percent			
MEYER-RIEMSLOH (1925)	VI 19	1		0	0	3		1	33	..	..	
	VI 20	2		2	100	7	1	0	0	1	16	
	VI 22	4		1	25	0	..	..	..	..	..	
KROPP (1927)	II 4	3		2	67	3		0	0	..	..	
USHER (1927)	III 1	3		1	33	4		0	0	..	..	
	III 3	2		1	50	3		0	0	..	..	
	III 7	2		1	50	7		0	0	..	..	
	III 32	2		1	50	2		0	0			
	III 34	3		1	30							
	III 35	1		1	100							
USHER (1927a)	III 10	4		3	75	6		0	0	..	..	
KAWAKAMI (1926)	III 5	3		1	33	5		2	40	..	..	
	II 4	1		1	100	1		0	0	..	..	
	II 7	2		1	50	0		..	..	..	..	
	III 19	4		2	50	3		1	33	..	..	
	III 26	3		2	67	5		2	40	..	..	
Grand Total		444	25	263		345	17	26				

a. LEBER (1871) found daughter unaffected. SCHILLING (1875) found daughter affected but gives no ophthalmoscopic findings (DREXEL 1922, p. 54)
b. NETTLESHIP, 1909 p. clxii, figure 87. DREXEL 1922, p. 107.
c. The daughter has atropic colored papillæ; narrow vessels.
d. Other sibs?
e. Atrophic opticus.
f. Two other children, sex unknown.
g. DREXEL expresses doubt if typical Leber's disease; 3 cousins show white papillæ.
h. Not all children of III 3 certainly known.
i. Other daughters affected left side, a central color section, papillæ red gray. Not typical ♀; one daughter shows absolute central scotom; also temporal half papilla white.
j. Daughter shows central scotom and opticus atrophy.
k. Mother's mother's brother affected.
l. One of 2 daughters examined ophthalmoscopically.

TABLE 2b

Incidence of hereditary opticus atrophy in progeny of specified matings. Mating II, F, normal; M, affected.

REFERENCES	Reference to Mother	SONS				DAUGHTERS				CONDUCTORS		Remarks
		No.	X or two	Affected		No.	X or two	Affected		No	Percent of fertile females	
				No.	Percent			No.	Percent			
HASWELL (1888)	II 2	7		6	86	2		..	..	2	100	a
SYM (1891)	I 2	3		3	100	2		0	0	2	100	b
BACH (1909)	II 2	3		3	100	1		0	0	1	100	
WAARDENBURG (1924)	IV 14	2		1	50							
MEYER-RIERISLOH (1925)	V 8	3	1	2	100	4	2	0	0	..	..	
IRONSIDE (1926)	II 1	2	..	2	100	3	..	0	0	..	..	
USHER (1927)	III 22	0		..		1	..	0	0			
KAWAKAMI (1926)	II 11	2		0	0	2		0	0	1	50	
	II 12	2		1	50	4		2	50	2	50	
	III 30	1		0	0	3		0	0	0	0	
	III 31	2		1	50	4		2	50	..	..	
Grand Total		27		19		26		4				

a. No special age data in unaffected son; did he die before age of onset of disease.

b. Mother affected at 51 years (after menopause).

TABLE 2c

Incidence of hereditary opticus atrophy in progeny of specified matings. Mating III. Father affected; M. genoytpically N.

REFERENCES	SONS					DAUGHTERS				CONDUCTORS		Remarks
	Reference to Mother	No.	X or two	Affected		No.	X or two	Affected		No.	Percent of fertile females	
				No.	Percent			No.	Percent			
HASWELL (1888)	III 1					2		0	0	..	..	a
	III 5											b
	III 9											c
	III 10											d
	III 11											e
	II 3											f
TAYLOR	IV 1	1		0	0	2		0	0	..	..	
GOULD (1893)	III 1											g
	V 5	0				1		0	0	..	..	
	V 9	4		0	0	2	..	0	0	..	..	
	V 23	0		0	0	2		0	0	..	..	
WESTHOFF (1895)	II 4	4		0	0	0	1	0	0	..	..	
	II 5	1		0	0	3		0	0	0	0	
RAYMOND (1898)	II 2	2		0	0	0	..	..	..	..	..	
HORMUTH (1900)	II 1	2		2	100	..	..	..	..	..	..	
BRAMWELL (1903)	II 1	1		0	0	3		0	0			
USHER (1906)	III 12	2		0	0	2		0	0			h
COSTE (1907)	II 4	1		0	0	1		0	0			
HANCOCK (1908)	I 1	3		0	0	3		0	0	2	67	i
	III 5	3		0	0	3		0	0			
	III 8	1		0	0							
	III 1	4		0	0	3		0	0			
EVANS (1909)	I 1	0				1		0	0			
	I 7	1		0	0	0		..	..	..	..	
	II 7	1		0	0	1		0	0			
RAYMOND AND KÖNIG	II 2	2		0	0							
TAYLOR AND HOLMES (1913 II)	II 15	2		0	0	2	1	0	0	..	..	
	II 2	5	2	0	0	1	0	0	0	..	..	
FLEISCHER AND JOSENHAUS	IV 6	4	0	0	0	0	0	0	0	..	..	

TABLE 2c (*continued*)

REFERENCES	Reference to Mother	SONS				DAUGHTERS				CONDUCTORS		Remarks
		No.	X or †♂	Affected		No.	X or †♂	Affected		No.	Percent of fertile females	
				No.	Percent			No.	Percent			
VOGT AND KNÜSEL (1922)	III 3	0	..	..	..	1	..	0	0	..	..	
	III 5	2	..	0	0	0	..	..	..	..	..	
GINSBERG (1923)	III 7	3	0	3	100	0	..	..	..	..	..	j
HIRSCH (1923)	III 7	2		0	0	4		0	0	..	..	
	III 8	1		0	0	2		0	0			
	III 10	2		0	0	2		0	0			
	IV 25	1		0	0	2		0	0			
WORTON (1913)	III 12	4		0	0	1		0	0	..	..	
	III 15	4		0	0	..		0	0	..	..	
WAARDENBURG (1924, I)	IV 3	0		..	..	2		0	0	..	..	
	IV 21	1		0	0	5		0	0			
MEYER-RIEMSLOH (1925)	VI 3	1		0	0	0	..	..	..	..	..	
	VI 10	0	..	..	..	2	..	0	0	..	..	
	VI 11	0	..	..	..	2	..	0	0	..	..	
IRONSIDE (1926)	II 2	4	..	0	0	6	..	0	0	..	..	
KROPP (1927)	II 1	2		0	0	3		2	67	..	..	k
USHER (1927, II)	III 4	6		0	0	4		0	0			
	III 8	1		0	0	1		0	0	..	..	
	IV 92	2		0	0	1		0	0	..	..	
	III 56	5		0	0	1		0	0	..	..	
USHER (1929, I)	II 5	1		1	0	1		0	0	0	0	
	III 17	2		0	0	2		0	0	0	0	l
Grand Total		39		5		41		2				

a. Also 4, sex unknown N.
b. 5, N, sex unknown.
c. 4, N, sex unknown.
d. 3, N, sex unknown.
e. 5, N, sex unknown.
f. 7, N, sex unknown.
g. 14 children, all N.
h. Also some additional daughters, unaffected.
i. The father (I 1) showed onset at 25 and later recovery, like grandsons!
j. Father and all 3 sons examined ophthalmoscopically, whitened papillæ.
k. "Diagnose von Lebersche familie Optikus atrophie nicht absolut sicher."
l. No grandchildren or other descendants affected.

TABLE 2d

Incidence of hereditary opticus atrophy in progeny of specified matings. Mating IV. F, affected; M, conductor.

REFERENCES	REFERENCE TO MOTHER	SONS				DAUGHTERS				
		No.	X or †yo	Affected		No.	X or †yo	Affected		Conductor
				No.	Percent			No.	Percent	
KAWAKAMI 1926	II 9	3		2	67	1		0	0	
Total		3		2		1		0		

TABLE 2e

Incidence of hereditary opticus atrophy in progeny of specified matings. Mating V. F, affected; M, affected.

REFERENCES	Reference to Mother	SONS				DAUGHTERS				CONDUCTORS		Remarks
		No.	X or †yo	Affected		No.	X or †yo	Affected		No.	Percent of fertile females	
				No.	Percent			No.	Percent			
WAARDENBURG (1924)	V 26	3		1	33	3		0	0	0	0	a
USHER (1927)	III 6	0				0						
Total		3		1		0		0				

a. Children mostly under 21; daughters probably under 15 years.

THE CORRELATION BETWEEN THE SEX OF HUMAN SIBLINGS. I. THE CORRELATION IN THE GENERAL POPULATION*

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INTRODUCTION

Of recent years problems of sex—variously designated as sex determination, sex inheritance, sex linkage, etc.—have been extensively investigated by experimental methods. Interest in this field of experimentation has perhaps diverted attention from the possibilities of the application of statistical methods to certain problems and to certain kinds of data for which experimental methods as conventionally understood can not readily be used. Quite obviously the two methods of research are not mutually exclusive. Both may contribute to a more complete understanding of a complex problem.

The purpose of this paper is to consider the correlation between the sex of human siblings by means of methods which, as far as we are aware, have not heretofore been applied to this problem.

The sex of human offspring is generally assumed to be distributed by chance except for the fact that the proportion of male and female births is not equal. Let n_m be the number of male births and n_f be the number of female births in families of a total size of $n_m+n_f=n$. It is generally sup-

* Part of the cost of the accompanying tables is paid by the GALTON AND MENDEL MEMORIAL FUND.

posed that if $p_m = \Sigma(n_m)/\Sigma(n)$ be the probability of male births and $p_f = \Sigma(n_f)/\Sigma(n)$ be the probability of female births, the chances of the $s+1th$ birth in any given family being male will be p_m no matter what the sex of the s preceding children.

If this assumption be true, the distribution of the sexes in N families of constant size, n, should be given by the terms of the point binomial $N(p_m+p_f)^n$, with standard deviation of number of males (or of females) $\sqrt{npqpq}$. GEISSLER as early as 1889 recognized the importance of taking $p_m > p_f$ and gave $(p_m+p_f)^n$ for large series of German families. NEWCOMB (1904) also employed point binomials for representing the distribution of the number of males and females in families, but took $p_f = p_m$.

If the empirical distribution of number of males (or females) per family of size n is to be compared with the theoretical distribution as given by the point binomial with a view to determining whether the discrepancies between the two distributions are larger than those to be expected as the result of random sampling, some statistical criterion of goodness of fit must be employed. PEARSON'S χ^2, P test (1900) and ELDERTON'S tables for testing goodness of fit (1924) were not available to GEISSLER, but FISHER (1925, pp. 69–71) has shown that in the case of GEISSLER'S families of eight children the value of P (the probability that deviations as large as or larger than those actually observed may be reasonably supposed to have arisen from random sampling, and not to be confused with p_m or p_f as defined above) is small and that the actual standard deviation is larger than the theoretical.

FISHER notes the possibility of the presence of identical twins influencing the variance, but while he finds this factor inadequate to explain the differences between the observed and the theoretical standard deviation, he does not pursue the point further. The obvious explanation is that the sex of the offspring of the same parents is not wholly independent, but correlated.

METHODS

Given a series of families each of n children, six procedures for determining whether the sex of the offspring is distributed at random among the siblings are theoretically available.

(1) The actual distribution of number of males (or females) per family of given size may be compared with the theoretical distribution provided by the point binomial, as indicated above.

(2) The statistical constants of the actual distribution of number of

males (or females) per family of given size may be compared with the constants for the theoretical distribution.

(3) The relationship between the sex of any two births each occupying a definite place, say the rth and the tth, may be determined by the use of the four-fold table

Sex of tth child

Sex of rth child	m	f	Total
m	n_{mm}	n_{mf}	$n_{mm}+n_{mf}$
f	n_{fm}	n_{ff}	$n_{fm}+n_{ff}$
	$n_{mm}+n_{fm}$	$n_{mf}+n_{ff}$	

and the calculation of the correlation by methods applicable to such tables.

The applicability of the method is limited by the fact that in general the sequences of the sexes of human siblings are not given in the data, but only the numbers of each sex.

(4) If there be n siblings per family and if each be used once as a first and once as a second member of a pair we may regard the family as constituting a class and may obtain a four-fold intra-class (HARRIS 1913) correlation table $\Sigma[n(n-1)]$ entries, where Σ denotes summation for the N available families.

Such four-fold tables for the sex of members of the same sibship may be readily formed by methods indicated in a paper on the correlation between the fates of seeds planted in the same hill (HARRIS and NESS 1928) or from the moments of the frequency distributions by formulae given elsewhere (HARRIS, GUNSTAD and NESS 1930). The relationship between the sex of the children of the same family may then be expressed in terms of PEARSON's equivalent probability correlation coefficient (1912).

(5) In cases in which the sex of any individual child, say the sth child, is definitely known and the total number of male and female children of the family is also available, the data may be represented in a bi-serial correlation surface, in which one variable is given in the alternative categories of male and female while the other is given in the quantitative terms of numbers of males or females in the $n-1$ remaining children of the family. Quite obviously such tables should be made for families of a given size, or precautions should be taken to express the number of males (or females) in the $n-1$ remaining children as ratios to $n-1$.

If the data permit this method of tabulation, it should be possible to

determine correlation coefficients by some modification of PEARSON'S bi-serial method (1909).

(6) If the sex of the siblings of definite birth order be unknown but merely the total number of each sex in sibships of a given size, tables which are fundamentally symmetrical in nature but bi-serial in form may be constructed by determining the relationship between the sex of each of the n children classed in alternative categories and the sex of the remaining $n-1$ children of families of constant size considered on the quantitative scale of number of males (or females) per $n-1$ offspring.

Here, as in case (5), bi-serial theory must be applied.

These methods fall quite obviously into two groups. The first (methods 1 and 2) test for the existence of correlation between the sex of the members of the same family by determining the deviation of the number of either sex actually observed from the theoretical number, and expresses the closeness of agreement on an improbability scale. The methods of the second group (methods 3–6) express the differentiation of the families with respect to the tendency to produce an excess above the theoretical frequencies of children of either sex in terms of the correlation between the sex of the members of the same sibship.

No mathematical assumption concerning the nature of the "frequency distribution" of the character sex is necessary in the use of the first method. Given the probabilities p_m and p_f the point binomial is rigidly applicable as an expression of the theoretical distribution, on the assumption that the sex of the offspring is wholly uninfluenced by genetic or physiological variables peculiar to the family in which the offspring are produced. Practical limitations in the use of this method will be indicated below.

In the case of the four methods of the second group, certain underlying assumptions are necessary. Such assumptions are unavoidable when data can not be recorded on a quantitative scale. The methods of the group fall into two classes. The first involves a 2×2-fold tabulation of the data, while the second involves a $2\times n$-fold arrangement of the data. These last two must be treated by the bi-serial theory. Since certain difficulties in the modification of the theory to adapt it fully to present needs are still to be overcome, these methods will not be further discussed in this paper.

The correlations based on four-fold tables must be determined by the classical four-fold r method of PEARSON, or by the newer equivalent probability method also proposed by PEARSON (1912). Since the first method assumes the normality of distribution of the two variables, it has seemed desirable to place our reliance on the equivalent probability method which

involves no assumption concerning the nature of the distribution. The calculation of the equivalent probability coefficient will be illustrated in greater detail below.

DATA ANALYZED AND RESULTS

The data here employed are drawn from the work of GEISSLER (1889), who has given records of the sex of 4,794,304 children. These are reported as born by 998,761 mothers, but these are weighted instead of actual numbers, since the full record of the mother and of her offspring is returned for each additional child reported during the ten year period 1876–1885. It must be noted that the series of families is not complete in that all cases in which only one child was born are omitted, and that the number of children is weighted, in that a mother who had borne two children before 1876 and who had borne three children during the decade would be recorded in families of three, four and five. These facts do not render the data unusable for present purposes, but it would be highly desirable to have the methods of analysis here developed applied to data for completed families—that is, to the records of numbers of children borne by mothers married for at least 20 or 25 years and having attained the age of 50 years.

Since GEISSLER's paper is relatively inaccessible we have rearranged his data to present the frequency distributions of number of males per family in the form of a correlation table between number of children born and number of males per family in table 1. All constants required in the present paper may be computed by the use of formulae to be given later from the data of this table.

Other series of data will be treated in a subsequent paper.

The frequency distribution of number of male children per family

The selection of the proper values of $p=\Sigma(n_m)/\Sigma(n)$ and $q=\Sigma(n_f)/\Sigma(n)$ to be used in calculating the terms of the point binomial presents no difficulty when only a single series of families of a given size is available, since the worker has no option but to use the actual numbers of each sex as given in his records. When families of different sizes are involved, the selection of the value of p requires some consideration.

GEISSLER determined the value of $p=0.514768$ by taking the 2,468,305 males and the 2,325,999 females of his families of from 2 to 30 children and adding to them the 114,609 males and the 108,719 females born as the first child in the families of two children. Thus he based his value of p on the 2,582,914 males out of the total 5,017,632 weighted births. The values of p and q thus determined he applied to families of from 2 to 12 children.

Elsewhere we have shown (HARRIS and GUNSTAD 1930) that there may

be objection to GEISSLER'S procedure in obtaining the number of males and females born in families of one child, but at this date our only alternative is to utilize the value $p = 0.514768$ as given by him for the whole series.

While on first consideration it might seem that the value of p' determined from all of the available data is the most suitable value to be employed in calculating the theoretical numbers of children of each sex in families of a given size (because of the fact that the errors of random sampling will be smaller for p' derived from the sample containing all the individuals than for the values of p derived from the sub-samples representing families of any given size) this is not perfectly clearly the case.

If the sex ratio changes with the size of the family (as has been suggested in the literature), the value of p will also change. If this be true the employment of one constant value of p for the whole series will result in the using of a value which is too low for certain ranges of size of family and too high for other ranges of number of children per family.

The alternative method of procedure is, of course, to determine the values of p independently from the data of families of each size.

As far as we are aware there is no *a priori* theory for deciding which of the two procedures is the more logical. All that can be done to settle the point is to determine whether the ratios of male births to total births changes significantly from smaller to larger families, or to express this same relationship in some other way. This problem has been investigated (HARRIS and GUNSTAD 1930) with the result that, for GEISSLER'S data at least, there is a small and irregular but statistically significant increase in the proportion of males from the smaller to the larger sibships.

The results in the first section of table 2 are obtained from the constant value $p' = 0.514768$ while those in the second section are computed from the values for each individual family as given under the caption p.

The values of p tend to increase from the smaller to the larger families. Thus the values of $p - p'$ are negative for families of from 2 to 8 children and positive for families of from 9 to 18 children considered individually and for families of 19 to 30 children considered as a group. The methods of determining the ratios of $p - p'$ to their probable errors, $E_{(p-p')}$, and the significance of the differences have been discussed elsewhere (HARRIS and GUNSTAD 1930) and need not be considered here. For our present purposes the demonstration of a systematic trend in the values of p is of importance because it justifies the comparison of the actual numbers of children with two binomial distributions, one based on p and the other on p'.

The deviations of the empirical distributions of the number of males per family from the point binomials are expressed in terms of χ^2 and P.

Notwithstanding the fact that the point binomials are calculated in two ways, the values of P are low throughout. When the constant values of p' derived from all available data are employed the chances of the discrepancies between the observed and the theoretical distributions having arisen through random sampling are in all cases but one less than 2 in one hundred thousand. In 13 out of the 17 comparisons they are less than 1 in a million. When the value of p is determined independently for each size of family the highest value of P is only 0.0013 while 12 of the 17 values are less than $1/10^6$. In evaluating these results for the series as a whole it must not be forgotten that there is a certain, and unknown, amount of weighting due to two or more inclusions of some individuals. Since the distributions are calculated independently for each size of family, this limitation can not apply to the individual values of χ^2 and P.

Before closing this section a limitation of this method must be noted. As the size of the family increases the frequencies are distributed among an increasing number of classes. Thus there is a tendency for the values of χ^2 to become abnormally large through the influence of two purely statistical factors. First, the actual numbers of children must be recorded in integers whereas the theoretical numbers as given by the binomial may be given in fractions. Thus the ratio of the squared deviations of the observed from the theoretical numbers to the theoretical numbers may be abnormally large. Second, in the largest families, one or more classes may have no empirical frequencies. In such cases the class contributes the theoretical number of males to the value of χ^2. It is for this reason that the point binomial has not been computed for families of over 18 children. For families of this size the values of χ^2 are unquestionably too high.

Expression of deviation of observed from theoretical distribution in terms of difference in variability

An alternative method of expressing the results is to compare the squared standard deviation (the variance) of the empirical and theoretical distributions with regard to their probable error. The theoretical variance for number of males per family for families of size n is

$$\sigma'^2 = \mu_2' = npq.$$

We require to compare the observed squared standard deviation, μ_2 with the theoretical by evaluating $(\mu_2 - \mu_2') \pm E(\mu_2 - \mu_2')$. Since μ_2', represents a theoretical distribution to be used as a basis of comparison we take its probable error to be 0, and determine

$$(\mu_2 \pm \mu_2') \pm E_{\mu_2}.$$

As is well known (PEARSON 1903)

$$E_{\mu_2} = 0.67449\frac{\mu_4' - \mu_2'^2}{N}$$

where for samples containing two alternative classes only

$$\mu_2' = npq$$

$$\mu_4' = 3n^2p^2q^2 + npq(1 - 6pq)$$

and

$$\mu_4' - \mu_2'^2 = 2n^2p^2q^2 + npq(1 - 6pq).$$

These are easily evaluated. The results are given in table 3.

Here the first two columns give the size of the family and the total number of families in each class. The third, fourth and fifth columns give the empirical (μ_2) and the theoretical (μ_2') values of the second moment coefficients and the differences. The sixth column gives the ratio of ($\mu_2 - \mu_2'$) to its probable error. The final column gives $1/2(1-\alpha)$ or the probability of deviations as large as or larger than those actually observed having arisen through the errors of random sampling.

Since SHEPPARD's tables of the probability integral (1902) do not give the values of deviation $>6\sigma$, we have had recourse to PEARSON's (1912) table vi giving $-\log F$, where $F = \frac{1}{2}(1-\alpha)$ as defined by Sheppard.

Without exception the values of $\mu_2 - \mu_2'$ are positive. Since in the table of the probability integral,

$$\tfrac{1}{2}(1 - \alpha) = \int_z^\infty \mathfrak{z}dx$$

gives the probabilities of deviation of the proportion of males as large as or larger than those actually observed having arisen through the errors of random sampling, a glance at the values in the final column of table 3 shows that the chances of obtaining through the errors of random sampling differences between μ_2 and μ_2' as large as those actually found are in general exceedingly small.

The correlation between the sex of two consecutive children of the same mother

In only one case do GEISSLER's (1889) data permit the determination of the correlation between the sex of two successive children of the same mother. This is possible in the case of families of two children. The frequencies for the 223,328 families and the routine of the correlation of the equivalent probability correlation coefficient are as follows.

Second Child

First Child	Male	Female	Totals
Male	n_{mm} 59518	n_{mf} 55091	114609
Female	n_{fm} 55196	n_{ff} 53523	108719
Totals	114714	108614	223328

$$\chi^2 = \frac{(n_{mm}n_{ff} - n_{mf}n_{fm})^2 \cdot N}{(n_{mm} + n_{fm})(n_{mf} + n_{ff})(n_{mm} + n_{mf})(n_{fm} + n_{ff})}$$

$$= \frac{(144779078)^2 \times 223328}{(12460175871)(12459546396)} = 30.1529$$

$$\frac{1}{2}(1 + \alpha_1) = \frac{n_{mm} + n_{mf}}{N} = \frac{114609}{223328} = 0.513$$

$$\frac{1}{2}(1 + \alpha_2) = \frac{n_{mm} + n_{fm}}{N} = \frac{114714}{223328} = 0.514.$$

Interpolating from PEARSON's table V,

$$\chi_{\alpha_1} = 1.2536 \quad \chi_{\alpha_2} = 1.2537$$

$${}_0\sigma_r = \frac{1}{\sqrt{N}}\chi_{\alpha_1}\chi_{\alpha_2} = \frac{(1.2536)(1.2537)}{\sqrt{223328}} = \frac{1.57163832}{472.5759} = 0.00333$$

$$r_p{}^2(=){}_0\sigma_r{}^2\chi^2 = (0.0000110889)(30.1529) = 0.00033436$$

$$r_p(=) + 0.0183.$$

The equivalent probability intra-class correlation between the sex of children of the same family

In the determination of the intra-class equivalent probability correlation coefficients the first task is the formation of the 2×2-fold table. This is accomplished by use of the method of an earlier paper (HARRIS, GUNSTAD and NESS 1930) as follows:

Let n_m be the number of male births, and n_f the number of female births in families of total size $n_m + n_f = n$. Then the frequencies of the 4-fold table

	Male	Female	Totals
Male	n_{mm}	n_{mf}	$n_{mm}+n_{mf}$
Female	n_{fm}	n_{ff}	$n_{fm}+n_{ff}$
Totals	$n_{mm}+n_{fm}$	$n_{mf}+n_{ff}$	$\Sigma[n(n-1)]$

may be written in terms of the first and second moments, and product moments of the variables.

$$n_{mm} = \Sigma[n_m(n_m - 1)] = \Sigma(n_m^2) - \Sigma(n_m)$$
$$n_{ff} = \Sigma[n_f(n_f - 1)] = \Sigma(n_f^2) - \Sigma(n_f)$$
$$n_{mf} = n_{fm} = \Sigma(n_f n_m) = \tfrac{1}{2}[\Sigma(n^2) - \Sigma(n_m^2) - \Sigma(n_f^2)].$$

Applying these formulae to the determination of the 2×2-fold table for the relationship between the sex of the members of 95,390 families of 6 children each, for which the frequency distribution of number of males is given in table 1, we obtain the distribution shown in the following table

Sex of "second" child

Sex of "first" child	Male	Female	Totals
Male	n_{mm} 758214	n_{mf} 712561	1470775
Female	n_{mf} 712561	n_{ff} 678364	1390925
Totals	1470775	1390925	2861700

The equivalent probability intra-class correlation may be determined (with a notation differing slightly from that used by PEARSON) as follows:

$$\chi^2 = \frac{(n_{mm}n_{ff} - n_{mf}^2)^2 \cdot N}{[(n_{mm} + n_{mf})(n_{mf} + n_{ff})]^2} = \frac{(6601903175)^2 \times 2861700}{(2045737716875)^2} = 29.8032$$

$$\frac{1}{2}(1 + \alpha_1) = \frac{1}{2}(1 + \alpha_2) = \frac{n_{mm} + n_{mf}}{N} = \frac{1470775}{2861700} = 0.514.$$

Interpolating from PEARSON's table V,

$$\chi_{\alpha_1} = \chi_{\alpha_2} = 1.2537$$

$$_0\sigma_r = \frac{1}{\sqrt{N}}\chi_{a_1}\chi_{a_2} = \frac{1.571764}{1691.6560} = 0.00093$$

$$r_p^2(=)_0\sigma_r^2 \cdot \chi^2 = (0.0000008649)(29.8032) = 0.00002578$$

$$r_p(=) + 0.0051$$

All of the data may be treated by the intra-class equivalent probability method. We have applied this procedure to individual families of 2 to 18 children, but have grouped together the results for the 141 families with 19 to 30 children, since the maximum number of any one of these classes is 77 for families of 19 children.

Table 4 gives the number of children per family, the frequency of each class of families, the entries (n_{mm}, n_{mf}, n_{fm}, and n_{ff}) of the four cells of the four-fold table, the value of χ^2 measuring the divergence between the actual frequencies and the theoretical frequencies of the four-fold distribution, and the equivalent probability correlation coefficients.

The correlation coefficients are of a very low order of magnitude, ranging from 0.0015 to 0.0824 but are positive in sign throughout. Since if there were no correlation between the sex of members of the same sibship the coefficients should be distributed about 0 with approximately equal numbers of positive and negative coefficients, we may note that if we ignore the magnitudes of the coefficients and consider only their uniform positive sign, we have about the same chance of obtaining these results by random sampling as of obtaining 18 consecutive heads in throwing a coin. This should occur about 4 times in a million.

The average values for the 17 coefficients for families of from 2 to 18 children is 0.0136. The coefficient for the 141 families with from 19 to 30 children is 0.0824. Combining all the data into a single four-fold distribution we find a coefficient of 0.0095.

The coefficient for the series as a whole is far lower than that for the families with from 19 to 30 children. It is quite probable that these very large families contain a relatively large proportion of twin births, many of which would be of the same sex. The low values for the series as a whole is determined by the enormous excess of records of families with small numbers of children. If we limit our attention to families of less than 9 children (for each class of which over 50,000 records are available) we find that the coefficients range from +0.0015 to +0.0182.

It is quite clear, therefore, that the sex of the members of the same family is not independent but correlated. Thus, certain parents have a definite tendency to produce families with a slight excess of males and

others to produce sibships with a slight excess of females, both beyond their theoretical frequencies as determined by laws of chance.

DISCUSSION, SUMMARY AND CONCLUSIONS

This paper, which is one of a series on the sex of human offspring, presents the results of an investigation of the distribution of the two sexes in large series of German families of various sizes and of the correlation between the sex of members of the same sibship.

It is shown that the distribution of the numbers of the two sexes in families of a given size is not strictly in accord with the theory that the sex of human offspring is determined wholly by chance, but that there is a significant deviation from a chance distribution.

Methods of expressing this deviation on the mentally comprehensible correlation scale are suggested. It is shown that when this is expressed in terms of intra-class equivalent probability correlation there is a very low positive relationship, of the order $r = 0.01$, between the sex of members of the same sibship.

With respect to the relative value of the two methods of analysis here suggested we may note the following considerations.

On first thought the comparison of the actual number of males or females in families with a given number of children with the theoretical number as given by the point binomial would seem to give the most critical and valuable criterion. This would seem to be true for two reasons. First, the assumptions underlying the application of these methods are of the simplest, most fundamental, and admittedly sound kind. Second, each frequency of the empirical distribution is compared with a corresponding frequency of the point binomial.

Against this procedure two objections must be urged. First, the χ^2, P test becomes less reliable as the ratio of the number of classes to the number of individuals included in the empirical series becomes larger. Second, the values of P are often so nearly infinitesimal that they are mentally incomprehensible and non-comparable from series to series. These defects are apparently both eliminated by expression of the results in terms of equivalent probability intra-class correlation.

In the present case the results obtained by the two methods are wholly consistent as far as the biological generalizations to which they lead are concerned and differ only in the form and numerical values of the expressions. The uniform consistency of results for families of all sizes rather than the ratios of the individual correlation coefficients to their probable errors provides the basis for confidence in the statistical significance of the results.

As an incidental result of the present investigation we may note that it establishes empirically the significance of small values of the correlation coefficient.

Biologists often assert that correlation coefficients of the order $r = 0.10$, $r = 0.20$, etc. are "insignificant," "meaningless," "of no value," or "worthless." This is in part due to the fact that some biologists have not yet grasped the idea that statistical constants are to be judged by their ratios to their probable error and not by their absolute magnitude. It is in part due to the failure of most biologists to realize that with extensive data and refined methods of analysis biology may be a highly exact science, and that in consequence relationships of a very low order may be expressed with a high degree of confidence as to their validity.

In our opinion hypotheses as to the biological interpretation of these findings as to matters of fact should be held in abeyance until further quantitative evidence of various kinds is available. A suggestion that immediately presents itself is that the series of data, while primarily composed of single births, contains a certain proportion of twins and presumably a small proportion of triplets. These are generally known to show an abnormally high proportion of individuals of the same sex. Thus an attempt might be made to explain the present correlation as due to the mixture of highly correlated and uncorrelated materials. A discussion of the influence of the presence of these multiple births on the correlations must be reserved for a subsequent paper.

Finally we must emphasize the fact that sex in man presents a highly complicated problem or group of problems. The sex of all zygotes can not be ascertained, but only the sex of those zygotes which develop to an age of several months. Thus the investigation of the problem of prenatal mortality is necessary to a full interpretation of the present statistical results. Here, as in many other fields of biological investigation, individual series of data generally fail to provide all the information required. We must be content to postpone synthetic work until we shall have available a sufficient range of constants derived from various sources to make sound conclusions possible.

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TABLE 1

Distribution of number of males per sibship in GEISSLER'S *series of 998761 (weighted) families.*

Number of Males	223328	179892	148903	120137	95390	72069	53680	38495	26500	16759	10690	6115	3332	1769	913	439	209	77	36	12	8	4	1	1	1	1	998761
21																						1					1
20																				1							1
18																					1						1
17																		1	1	..	1	1					4
16																1	3	..	1	1	..	1					7
15																3	2	6	..	..	2						13
14													1	2	8	5	6	1	2	..	..						25
13												4	11	21	21	23	14	6	3	2	..						105
12											7	24	60	49	40	32	15	8	5	3	1						244
11										14	60	108	146	109	80	44	20	7	4	1	1	1					595
10									43	159	298	338	276	203	117	68	34	8	6	3	1			1	1	1	1557
9								138	397	665	799	629	409	252	149	91	50	18	8				1				3606
8							342	981	1542	1611	1398	987	566	348	190	82	29	9	1								8086
7						786	2092	3204	3567	2899	2033	1234	675	335	137	46	14	6	1	1	1						17031
6					1943	4739	6678	6687	5674	3733	2360	1251	575	218	88	21	13	4	1								33985
5				4459	9933	12589	11929	9632	6363	3562	1821	849	328	145	48	12	6	2	1								61679
4			10634	20085	23274	20149	14959	9035	4868	2445	1198	428	173	53	20	6	..										107327
3		24923	38903	38665	30084	19103	10649	5652	2714	1164	521	182	88	19	8	3	3		2								172683
2	59518	68974	56025	36648	20736	10683	5331	2456	1058	405	160	69	20	12	5	2		1									262103
1	110287	65063	34705	16851	8012	3479	1485	630	239	89	29	10	4	2	1												240886
0	53523	20932	8636	3429	1408	541	215	80	35	13	6	2	..	1	1												88822
	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	27	28	29	30	

Number of Children per Family

TABLE 2

Values of χ^2 and P measuring the divergence of numbers of males from the numbers calculated from the point binomial on the basis of the value of p for individual families and on the basis of p′ for the whole series.

SIZE OF FAMILIES	NUMBER OF FAMILIES	CONSTANT p′			VARIABLE p			
		χ^2	P	p	$p-p'$	$p-p'/E_{p-p'}$	χ^2	P
2	223328	33.4387	.000000	.513422	−.001346	2.79	30.1547	.000000
3	179892	17.3975	.000601	.514716	−.000052	0.12	17.3862	.000604
4	148903	31.9469	.000004	.513757	−.001011	2.46	29.4160	.000007
5	120137	29.4945	.000019	.514041	−.000727	1.78	28.1743	.000035
6	95390	53.0014	.000000	.513951	−.000817	1.94	51.9114	.000000
7	72069	46.7716	.000000	.514648	−.000120	0.27	46.7392	.000000
8	53680	91.8993	.000000	.514677	−.000091	0.18	91.8965	.000000
9	38495	84.5168	.000000	.515039	+.000271	0.49	84.2706	.000000
10	26500	78.8680	.000000	.517494	+.002726	4.27	71.7229	.000000
11	16759	68.5036	.000000	.516895	+.002127	2.75	65.1896	.000000
12	10690	92.8036	.000000	.516830	+.002062	2.21	100.0275	.000000
13	6115	80.4336	.000000	.519026	+.004258	3.58	74.5460	.000000
14	3332	136.8569	.000000	.520215	+.005447	3.50	125.2893	.000000
15	1769	75.6104	.000000	.521688	+.006920	3.35	91.6556	.000000
16	913	164.0801	.000000	.521495	+.006727	2.41	148.0915	.000000
17	439	56.7651	.000008	.535710	+.020942	5.36	40.5625	.001291
18	209	76.8111	.000000	.526581	+.011813	2.15	55.0391	.000038
19–30	141	..	..	.527866	+.013098	2.06	..	..

TABLE 3

Comparison of actual variance ($\mu_2=\sigma^2$) of number of males per family with theoretical variance ($=npq$).

SIZE OF FAMILY	NUMBER OF FAMILIES	μ_2	μ_2'	$\mu_2-\mu_2'$	$E(\mu_2-\mu_2')$	$\frac{\mu_2-\mu_2'}{E(\mu_2-\mu_2')}$	$\frac{1}{2}(1-\alpha)$
2	223328	.505447	.499640	+.005807	.000714	8.14	21×10^{-9}
3	179892	.757856	.749350	+.008506	.001377	6.18	15×10^{-6}
4	148903	1.008960	.999243	+.009717	.002139	4.54	11×10^{-4}
5	120137	1.253921	1.249014	+.004907	.003075	1.60	14×10^{-2}
6	95390	1.523017	1.498832	+.024185	.004226	5.72	57×10^{-6}
7	72069	1.790443	1.748498	+.041945	.005753	7.29	44×10^{-8}
8	53680	2.067417	1.998277	+.069140	.007697	8.98	67×10^{-11}
9	38495	2.370400	2.247964	+.122436	.010300	11.89	14×10^{-17}
10	26500	2.655890	2.496940	+.158950	.013882	11.45	52×10^{-16}
11	16759	2.957159	2.746860	+.210299	.019300	10.90	89×10^{-15}
12	10690	3.339853	2.996601	+.343252	.026472	12.97	1×10^{-18}
13	6115	3.633895	3.245294	+.388601	.038038	10.22	26×10^{-13}
14	3332	4.260543	3.494279	+.766264	.055649	13.77	71×10^{-22}
15	1769	4.409851	3.742944	+.666907	.082019	8.13	21×10^{-9}
16	913	4.836813	3.992607	+.844206	.122054	6.92	15×10^{-7}
17	439	4.965750	4.228322	+.737428	.186810	3.95	39×10^{-4}
18	209	5.742376	4.487282	+1.255094	.287780	4.36	16×10^{-4}

TABLE 4

Frequencies for 2×2-fold intra-class correlation tables, values of χ^2 derived from four-fold table, and equivalent probability coefficient (r_p) measuring the correlation between the sex of members of the same family.

SIZE OF FAMILIES	NUMBER OF FAMILIES	FREQUENCY OF 2×2-FOLD TABLE				χ^2	r_p
		n_{mm}	n_{mf}	n_{fm}	n_{ff}		
2	223328	119036	110287	110287	107046	60.3034	.0182
3	179892	287486	268074	268074	255718	34.7723	.0089
4	148903	473076	444924	444924	423912	18.7725	.0051
5	120137	635486	599622	599622	568010	2.3159	.0015
6	95390	758214	712561	712561	678364	29.8032	.0051
7	72069	804734	753052	753052	716060	48.3909	.0063
8	53680	800000	747161	747161	711758	73.4430	.0078
9	38495	739934	687570	687570	656566	128.4641	.0107
10	26500	642916	591308	591308	559468	119.3125	.0111
11	16759	496068	456822	456822	433778	108.0492	.0120
12	10690	380588	348701	348701	333090	153.0095	.0164
13	6115	259356	235764	235764	223056	94.9359	.0157
14	3332	166666	148805	148805	142148	172.5552	.0265
15	1769	102284	91518	91518	86170	60.1719	.0200
16	913	60362	53908	53908	50942	43.5393	.0222
17	439	34592	29376	29376	26064	14.1875	.0172
18	209	17996	15681	15681	14596	17.3119	.0259
19–30	141	15636	12737	12737	12804	148.0288	.0824
2–30	998761	6794430	6307871	6307871	5999550	927.5633	.0095

THE INHERITANCE OF DORMANCY AND PREMATURE GERMINATION IN MAIZE*

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INTRODUCTION

Seeds of maize and in fact those of the majority of spermatophytes normally do not germinate during their period of development. Dormancy during this period is as essential to the perpetuation of the species as the ability to germinate after development has been completed. In maize, however, it has been found that the presence in the germplasm of various genetic factors results in germination, before the seed is mature, in certain definite proportions of the seeds. This condition has been reported and described by LINDSTROM (1923), EYSTER (1924a, 1924b), and by the writer (MANGELSDORF 1923, 1926). In the paper last cited, evidence was presented to show that a number of genetic factors are involved in the inheritance of premature germination in maize; that these factors operate at various stages in the development of the seed and differ in some of their effects. All are alike, however, in forcing the seed to germinate before development has been completed and hence, under natural conditions, are ultimately lethal in effect.

The present paper represents further studies on the inheritance of

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several forms of premature germination previously reported; the verification of several hypotheses which had been tentatively presented; and a study of new types more recently discovered. The studies reported here were made at the CONNECTICUT EXPERIMENT STATION from 1921 to 1926 and at the TEXAS EXPERIMENT STATION from 1927 to 1929. Some of the stocks used were found to be unadapted to Texas conditions and rather than delay completion of the work until new stocks could be developed, most of the F_3 progenies were grown in New Haven, the self-pollinated ears being returned to Texas for classification. I take this opportunity of thanking Doctor D. F. JONES and Doctor W. R. SINGLETON for their kindness in growing and pollinating this F_3 material. I wish also to acknowledge the assistance of Mr. A. T. CHISHOLM in classifying some 54,000 individuals included in these studies.

ORIGIN AND DESCRIPTION OF CHARACTERS

The origin and description of a number of these characters has already been given in a previous paper (MANGELSDORF 1926); consequently only a brief resumé need be included here. The reader is referred to the above paper for further details.

gc1

This is the first type of premature germination found. It was first noted in the second generation of inbreeding of a strain of Gold Nugget flint corn. Germination begins when the seeds are in the late milk stage and is associated with complete lack of color in the endosperm and chlorophyll in the plumule, except in the absence of light, when the plumule develops a faint tinge of bluish green. This character is inherited as a simple Mendelian recessive.

gc2

This character was found in an inbred strain of Golden Bantam sweet corn. Germination begins when the seeds are in the dough stage. The endosperm color is slightly affected but the plumules are normal green. This character is associated with small seeds which are defective in appearance and it may be that the premature germination is merely a secondary effect of a factor for defective seeds, since early germination of some of the hereditary types of defective seeds is by no means uncommon.

gc3

This stock was obtained from Doctor E. W. LINDSTROM and is the same one reported by him in 1923. It originated in an inbred strain of

Golden Bantam in the third generation of inbreeding. Germination begins at a very early stage and is almost completely associated with absence of color in the endosperm and lack of chlorophyll in the plumule. The g_{e3} type can be distinguished from g_{e1} only when both develop in darkness in which case the former is completely albinitic while the latter shows a faint greenish tinge. It is inherited as a simple recessive.

g_{e4}

An open-pollinated ear of flint corn of the Longfellow type received from Mr. T. B. MACAULAY of Montreal, Canada, gave rise to this type. Germination begins in the hard dough stage. Chlorophyll development is not affected and the endosperm color is only slightly diluted. The character is inherited as a simple recessive.

g_{e5}

This type of premature germination first appeared in the F_2 endosperm generation of a cross between g_{e1} and g_{e3}. It has since appeared in this same cross when repeated and in another cross in which g_{e3} was used as one of the parents. This situation is difficult to explain as the g_{e3} stock has always segregated in a normal 3:1 ratio. In appearance, g_{e5} differs in no discernible details from g_{e3}. Germination begins in the early milk stage and is associated with complete absence of endosperm and chlorophyll color.

g_{e6} g_{e7}

This character is due to the expression of duplicate factors. It was found in ears of an F_1 hybrid of two inbred strains of Canada Flint, neither of which had ever shown premature germination. Germination begins at the late dough stage. The plumule is green while the endosperm color is diluted only in small areas of the seed usually adjacent to the embryo. This character is inherited in a 15:1 ratio when both factor pairs are heterozygous; in a 3:1 ratio when one pair is homozygous recessive, the other heterozygous.

g_{e8} g_{e9} g_{e10}

A cross of an inbred strain of Sanford White flint with an unknown yellow flint gave rise to this stock. Germinating seeds were found in the F_2 endosperm generation in the ratio of 8:1. This was tentatively explained as the result of duplicate factors in the same linkage group. Later studies indicate that triplicate factors are involved and that two of these are linked. Germination begins at a very late stage and has no effect on chlorophyll development and practically none on endosperm color.

g_{e11}

This type of premature germination was first noted in the F_2 endosperm generation of a cross between two inbred stocks segregating for defective seeds, d_{e5} and d_{e11}, which later proved to be genetically identical. One parent was an inbred strain of Clarage Dent obtained from Mr. M. T. MEYERS, the other a strain of Reid's Yellow Dent from Doctor J. R. HOLBERT. Germinating seeds had never been noted in either of the parents, and since these were being studied especially for endosperm defects, it seems improbable that premature germination could have occurred without being noted. This type of premature germination is very striking in appearance, both the seed and plumule showing a pink color. The character appears to be inherited as a simple recessive.

g_{e12} g_{e13} g_{e14} g_{e15}

Ratios of 255:1 and 63:1 in several crosses indicate a set of quadruplicate factors all of which must be present in a homozygous recessive condition in order for premature germination to occur. Germination does not take place until the seed is practically mature and is later than in any of the other types described. The plumule seldom ruptures the pericarp and chlorophyll and endosperm color are not at all affected. The sprouting is so slight that the seeds must be rather carefully examined from the germ side in order to identify the recessives.

g_{ex}

This character is tentatively designated g_{ex} because little is known concerning it and it may prove to be identical with one of the types already described. It appeared in the F_2 endosperm generation of a cross between g_{e1} and g_{e6} g_{e7}, and was inherited as a simple recessive. In appearance it resembles g_{e4} rather closely and the two may prove to be genetically identical.

Peculiar origin of germinating seeds

An unusual fact regarding the origin of a large proportion of the types of premature germination is that they did not appear in the first generation of inbreeding when recessive characters are usually brought to light. Seeds of g_{e1} were first noted in the second generation; g_{e3} was discovered, according to LINDSTROM (1923), in the third generation; g_{e5} appeared only when g_{e3} was crossed with other stocks; g_{e11} resulted from a cross between two inbred strains which had never segregated for germinating seeds; and g_{ex} arose in a cross of g_{e1} g_{e6} g_{e7}. In addition g_{e6} g_{e7}, g_{e8} g_{e9} g_{e10}, and g_{e12} g_{e13}

g_{e14} g_{e15} were found in crosses, the parents of which had never shown these particular types of premature germination. These types, however, belong to a different category. They are the result of duplicate, triplicate, or quadruplicate factors and their occurrence in crosses is readily explained by assuming that the parents of the crosses were of such a genetic constitution that segregation could not occur. For example, the most simple explanation of the appearance of g_{e6} g_{e7} is that one parent was of the constitution g_{e6} g_{e6} G_{e7} G_{e7}, the other parent G_{e6} G_{e6} g_{e7} g_{e7}. Neither parent would segregate, nor would the F_1 seeds. In the F_2 generation, however, segregation in the ratio of 15:1 would be expected.

Such an explanation, however, does not account for the appearance of types which are inherited as simple recessives, such as g_{e1}, g_{e3}, g_{e5}, g_{e11} and g_{ex}. They might be the result of recent mutations but, if this is true, it is certain that mutations which result in premature germination are considerably more frequent than those of any other type so far observed in maize.

RESULTS OF CROSSING VARIOUS TYPES OF PREMATURE GERMINATION

The ultimate proof that all the types of premature germination, described above, are genetically distinct, must rest on the results of crosses in which the stocks are combined in all possible combinations. This program has not yet been completed but the data from such crosses as have been made, together with evidence of another nature, indicate rather convincingly that at least fifteen factors are involved in the inheritance of premature germination. The evidence for this conclusion is presented in the following pages.

Method of making crosses

Perhaps a word should be said here regarding the method used in crossing the stocks. Since all these characters are lethal they can be perpetuated only in the heterozygous condition. When dormant seeds from a segregating ear are planted, part of the plants thus produced are heterozygous; the remainder are homozygous dormant, the proportion depending upon the number of heterozygous factor pairs involved in the expression of the recessive condition. There is no way of distinguishing the two genotypes until several weeks after pollination. Consequently, the practice has usually been to pollinate at random at least five plants of one parent with pollen collected at random from five or more plants of the other parent. This practically insures that heterozygous plants of both parents are included but renders it impossible to predict the proportions in which the

various types of segregating progenies should appear in F_2 of any particular cross.

Method of presenting data

In all cases where crosses have been made, the two parental types of premature germination have reappeared in the F_2 endosperm generation which is borne on F_1 plants. The data from this generation are presented in detail and there appears to be no necessity for including the data on inheritance of the same characters in the parental stocks. The latter are therefore omitted except in the case of g_{e11} which has not yet been used in crosses.

When several types of segregating progeny occur in F_2 the different progenies have been grouped according to the Mendelian ratio which they fit most closely. Such an arbitrary grouping may be subject to errors, as SIRKS (1926) has pointed out, and the chief object in presenting the F_2 data in detail is that of demonstrating how large a proportion of the progenies fit a certain ratio within the limits of sampling errors, but differ significantly from other ratios which occur in the same population.

The fact that the segregation in any given progeny fits a particular Mendelian ratio does not, of course, prove that this ratio is the true expression of the segregation. Data collected at random are almost certain to fit one of the many possible Mendelian ratios within the limits of sampling errors. The behavior of the F_3 progenies, however, should show definitely whether any F_2 progeny has been correctly classified. F_3 progenies have been grown from F_2 populations representative of almost every ratio which occurred.

In tabulating the F_3 data it has not been considered necessary to present the data from each progeny separately. The progenies have been grouped, by simple inspection, according to the ratios which they appear to fit most closely. Some of the progenies might fall into either of two groups almost equally well but in general the groups have been well-defined with little overlapping. In addition the "goodness of fit" of each array has been calculated and with few exceptions was found to be reasonably close. The F_3 data indicate that such F_2 progenies as were tested had been correctly classified with regard to Mendelian ratios.

Results in F_2

$g_{e1} \times g_{e3}$

Since both of these characters are simple recessives it would be expected that the F_2 endosperm generation should produce two types of segregating

progenies, some segregating 3:1 and others segregating 9:7. In a previous cross of these two characters (MANGELSDORF 1926) these two types reappeared in F_2, but in addition a third group, segregating in a ratio of 27:37, also occurred. This is difficult to explain since both parental stocks had previously segregated in a ratio of 3:1. The cross was, therefore, repeated with the results shown in table 1. The situation is almost identical to that found previously. Three types of segregating progeny appeared and these grouped themselves definitely into 3:1, 9:7, and 27:37 ratios. We must conclude that three factors for premature germination are involved in thiscross. These are apparently independent intheir inheritance, no evidence of linkage being exhibited. The third factor is presumably the one which has already been designated as g_{e5}. Its effects are practically identical to those of g_{e3}

Ratios of 3:1 and 9:7 are expected from this cross if two pairs of complementary factors are involved. Table 2 shows that these requirements

TABLE 1

Segregating F_2 progenies of the cross $g_{e1} \times g_{e3}$.

EAR NUMBER	GENETIC FACTORS	PROBABLE RATIO	TOTAL SEEDS	NUMBER GERMINATING	THEORETICAL NUMBER GERMINATING	DEVIATION
2986	g_{e1}, g_{e3}, or g_{e5}	3:1	259	63	64.8	−1.8± 4.7
2987	"	"	281	75	70.2	4.8± 4.9
2990	"	"	271	76	67.8	8.2± 4.8
2991	"	"	251	57	62.8	−5.8± 4.6
2993	"	"	268	67	67.0	.. ..
2994	"	"	221	53	55.2	−2.2± 4.3
2995	"	"	192	42	48.0	−6.0± 4.1
Total			1743	433	435.8	−2.8±12.2
2988	g_{e1} and g_{e3} or g_{e5}	9:7	270	111	118.1	−7.1± 5.5
2996	"	"	199	84	87.3	−3.3± 4.7
2997*	"	"	284	125	124.3	.7± 5.6
2988	"	"	203	89	88.8	.2± 4.8
Total			956	409	418.2	−9.2±10.4
2989+	g_{e1}, g_{e3}, g_{e5}	27:37	291	166	168.2	−2.2± 5.7
2992	"	"	224	132	129.5	2.5± 5.0
Total			515	298	297.7	.3± 7.6

* See table 12 for F_3 progenies of this ear.

\+ See table 13 for F_3 progenies of this ear.

$g_{e1} \times g_{e4}$

have been met. Three ears proved to be segregating for g_{e1}, two ears for g_{e4}, and the remaining three ears for both characters. The di-hybrid ears all show a close approximation to a 9:7 ratio, indicating that the two factors are independent in their inheritance. It is noted that two ears segregating in an approximate ratio of 255:1 are included in table 2. These are discussed later.

TABLE 2

Segregating F_2 progenies of the cross $g_{e1} \times g_{e4}$.

EAR NUMBER	GENETIC FACTORS	PROBABLE RATIO	TOTAL SEEDS	NUMBER GERMINATING	THEORETICAL NUMBER GERMINATING	DEVIATION
2969	g_{e1}	3:1	303	71	75.8	-4.8 ± 5.1
2972	"	"	237	48	59.3	-11.3 ± 4.5
2977	"	"	249	68	62.3	5.7 ± 4.6
Total			789	187	197.3	-10.3 ± 8.2
2970	g_{e4}	3:1	342	86	85.5	$.5 \pm 5.4$
2978	"	"	269	78	67.2	10.8 ± 4.8
Total			611	164	152.7	11.3 ± 7.2
2971	g_{e1}, g_{e4}	9:7	279	130	122.1	7.9 ± 5.6
2973	"	"	221	91	96.7	-5.7 ± 5.0
2975	"	"	315	145	137.8	7.2 ± 5.9
Total			815	366	356.6	9.4 ± 9.6
2974*	g_{e12}, g_{e13}, g_{e14}, g_{e15}	255:1	268	1	1.05	$-.05 \pm .69$
2976	"	"	266	2	1.04	$.96 \pm .69$
Total			534	3	2.09	$.91 \pm .97$

* See table 18 for F_3 progenies of this ear.

$g_{e1} \times g_{e6} g_{e7}$

Since g_{e6} g_{e7} are duplicate factors which result in ratios of 15:1 when both pairs are heterozygous, this cross should produce three types of segregating progenies; 3:1, 15:1, and 45:19. The last is actually the trihybrid ratio 45:15:3:1 in which the three last terms are combined because the three phenotypes are so nearly alike that accurate classification

is difficult. Occasionally it has been possible to separate the g_{e1} and g_{e6} g_{e7} seeds on the same ear but generally all germinating seeds have been grouped together into a single class.

The results of this cross are set forth in table 3. It is evident that all three types of segregating progenies have appeared and hence the two stocks are distinct in their factors for premature germination. The close agreement between the theoretical and actual ratios indicates further that these three factors are independently inherited.

TABLE 3

Segregating F_2 progenies of the cross $g_{e1} \times g_{e6}g_{e7}$.

EAR NUMBER	GENETIC FACTORS	PROBABLE RATIO	TOTAL SEEDS	NUMBER GERMINATING	THEORETICAL NUMBER GERMINATING	DEVIATION
2954	g_{e1}	3:1	185	48	46.2	1.8±4.0
2955	"	"	256	58	64.0	−6.0±4.7
2958	"	"	105	22	26.2	−4.2±3.0
2964	"	"	272	70	68.0	2.0±4.8
Total			818	198	204.5	−6.5±8.4
2950	g_{e2}	3:1	284	72	71.0	1.0±4.9
2957	"	"	281	74	70.2	3.8±4.9
Total			565	146	141.2	4.8±6.9
2949	g_{e6} g_{e7}	15:1	205	13	12.8	.2±2.3
2953	"	"	227	13	14.2	−1.2±2.5
2961	"	"	132	10	8.3	1.7±1.9
2962	"	"	129	12	8.1	3.9±1.9
Total			693	48	43.3	4.7±4.3
2948	g_{e1}, g_{e6}, g_{e7}	45:19	297	92	88.2	3.8±5.3
2951	"	"	348	100	103.3	−3.3±5.8
2956	"	"	169	57	50.2	6.8±4.0
2960	"	"	33	12	9.8	2.2±1.8
Total			847	261	251.5	9.5±9.0
2947*	g_{e1}, g_{e2}, g_{e6} g_{e7}	135:121	233	114	110.2	3.8±5.1
2952†	g_{e12} g_{e13} g_{e14} g_{e15}	255:1	281	1	1.10	−.10±.71
2963	"	"	171	1	.67	.33±.55
Total			452	2	1.77	.23±.89

* See table 16 for F_3 progenies of this ear.

† See table 18 for F_3 progenies of this ear.

In addition to the expected ratios, three types of segregating progenies, which had not been anticipated, were encountered in this cross. Two ears were found to be segregating in a ratio of 3:1 for a character which obviously was not g_{e1}. The recessive seeds on these ears did not lack endosperm color as do seeds of g_{e1}, but resembled more nearly the recessive seeds of g_{e6} g_{e7}. This situation might be readily explained by assuming that part of the plants of the original g_{e1} stock were homozygous recessive for either the g_{e6} or g_{e7} factor pair. This explanation is not tenable, however, because of a second unexpected progeny, Ear No. 2947, which segregates in a ratio of 135:121. This ratio does not differ significantly from a 9:7 but the F_3 progenies presented later show beyond doubt that the segregation is not 9:7.

This cross, then, as did that between g_{e1} and g_{e3}, has resulted in the unexpected appearance of a new type of premature germination not previously observed in either parent. The new character is tentatively designated as g_{ez} until it can be studied further. In appearance it is practically identical to g_{e4} and may prove to be the same genetically.

TABLE 4

Segregating F_2 progenies of the cross $g_{e4} \times g_{e3}$.

EAR NUMBER	GENETIC FACTORS	PROBABLE RATIO	TOTAL SEEDS	NUMBER GERMINATING	THEORETICAL NUMBER GERMINATING	DEVIATION
3008	g_{e3}	3:1	216	52	54.0	−2.0±4.3
3009	"	"	258	61	64.5	−3.5±4.7
3012	"	"	194	61	48.5	12.5±4.1
3016	"	"	300	76	75.0	1.0±5.1
3017	"	"	186	43	46.5	−3.5±4.0
3019	"	"	242	57	60.5	−3.5±4.5
Total			1396	350	349.0	1.0±10.9
3013	g_{e4}	3:1	259	71	64.8	6.2±4.7
3014	"	"	142	42	35.5	6.5±3.5
3015	"	"	252	63	63.0	..
3018	"	"	101	35	25.2	9.8±2.9
3020	"	"	239	71	59.8	11.2±4.5
3021	"	"	304	78	76.0	2.0±5.1
Total			1297	360	324.3	35.7±10.5
3010	g_{e3} g_{e4}	9:7	272	120	119.0	1.0±5.5
3011	"	"	130	51	56.9	−5.9±3.8
Total			402	171	175.9	−4.9±6.7

This cross, too, has produced two ears segregating in a ratio of approximately 255:1. These are discussed later.

$$g_{e3} \times g_{e4}$$

Two types of segregating progenies, approximating 3:1 and 9:7 ratios, are expected from this cross. Both of these types have been obtained as shown in table 4. The ears segregating in a 3:1 ratio have been further subdivided into two groups, those segregating g_{e3} and g_{e4}. Such a separation is possible in this cross because of the marked phenotypical difference in the two characters.

The only significant deviation in the data is a slight excess of recessives in the six ears which segregate for g_{e4}. One of these ears shows a deviation of 3.4 times the error and the deviation for the group is also 3.4 times the error. With this exception the data are in close agreement with the theoretical ratios and indicate that g_{e3} and g_{e4} are genetically distinct and independently inherited.

TABLE 5

Segregating F_2 progenies of the cross $g_{e3}\ g_{e7} \times g_{e3}$.

EAR NUMBER	GENETIC FACTORS	PROBABLE RATIO	TOTAL SEEDS	NUMBER GERMINATING	THEORETICAL NUMBER GERMINATING	DEVIATION
3046	g_{e3}	3:1	198	44	49.5	−5.5±4.1
3045	$g_{e3}\ g_{e7}$	15:1	230	13	14.4	−1.4±2.5
3048*	"	"	268	13	16.8	−3.8±2.7
3050	"	"	276	14	17.2	−3.2±2.7
3052	"	"	257	11	16.1	−5.1±2.6
3053	"	"	260	9	16.2	−7.2±2.6
3056	"	"	268	15	16.8	−1.8±2.7
Total			1559	75	97.4	−22.4±6.4
3049	g_{e3}, $g_{e3}\ g_{e7}$	45:19	246	82	73.0	9.0±4.8
3051	"	"	285	105	84.6	20.4±5.2
3055	"	"	246	76	73.0	3.0±4.8
3057	"	"	240	70	71.3	−1.3±4.8
Total			1017	333	302.0	31.0±9.8
3047	$g_{e3}\ g_{ex}$	9:7	243	99	106.3	−7.3±5.2
3054	"	"	137	61	59.9	1.1±3.9
Total			380	160	166.2	−6.2±6.5

* See table 14 for F_3 progenies of this ear.

$g_{e3} \times g_{e6}\ g_{e7}$

The results of this cross should be similar to those from the cross $g_{e1} \times g_{e6}\ g_{e7}$ in producing Mendelian ratios of three types, 3:1, 15:1, and 45:19. One ear of the first, six of the second, and four of the third were found, as shown in table 5. These were identified not only by the proportion of recessives but also by phenotypical differences in the two types of premature germination. The data show only a fair agreement with the theoretical ratios. Each of the six ears segregating in a 15:1 ratio shows a slight but not significant deficiency of recessives, while the total deviation for the group is 3.5 times the error.

This excess in ears which are segregating for all three factors may indicate linkage between g_{e3} and one member of the $g_{e6}\ g_{e7}$ pair, especially

TABLE 6

Segregating F_2 progenies of the cross $g_{e4} \times g_{e6}\ g_{e7}$

EAR NUMBER	GENETIC FACTORS	PROBABLE RATIO	TOTAL SEEDS	NUMBER GERMINATING	THEORETICAL NUMBER GERMINATING	DEVIATION
3044A	g_{e4}	3:1	285	71	71.2	−.2±4.9
3030	$g_{e6}\ g_{e7}$	15:1	255	17	15.9	1.1±2.6
3032	"	"	260	26	16.2	9.8±2.6
3034	"	"	52	4	3.3	.7±1.2
3035	"	"	226	20	14.1	5.9±2.5
3036	"	"	180	12	11.2	.8±2.2
3038	"	"	267	25	16.7	8.3±2.7
3039	"	"	294	12	18.4	−6.4±2.8
3040	"	"	259	20	16.2	3.8±2.6
3043	"		269	20	16.8	3.2±2.7
Total			2062	156	128.9	27.1±7.4
3033*	g_{e4}, $g_{e6}\ g_{e7}$	45:19	262	87	77.8	9.2±5.0
3037	"	"	92	27	27.3	−.3±3.0
3044B	"	"	212	68	62.9	5.1±4.5
Total			566	182	168.0	14.0±7.3
3031	$g_{e12}\ g_{e13}\ g_{e14}$	63:1	90	1	1.4	−.4±0.8
3041†	"	"	122	2	1.9	.1±0.9
3042	"	"	219	5	3.4	1.6±1.2
Total			431	8	6.7	1.3±1.7

* See table 15 for F_3 progenies of this ear.

† See table 17 for F_3 progenies of this ear.

in view of the fact that ears of the same cross, but segregating for either character alone, were deficient in recessives.

This cross has, like that of $g_{e1} \times g_{e3}$, yielded an unexpected type of ratio. Two ears are clearly segregating in a ratio of 9:7 and all of the recessives on these ears are of the g_{e3} type. Apparently the g_{e5} factor postulated in the cross of $g_{e1} \times g_{e3}$ is also present in this cross. Since both crosses have g_{e3} in common as one parent it seems very probable that this extra factor is in some way contributed by the g_{e3} stock.

$g_{e4} \times g_{e6}$ g_{e7}

This cross, like the one immediately preceding, should produce three types of segregating progenies; 3:1, 15:1, and 45:19. All of these occur and the data agree fairly well with the theoretical ratios (see table 6). In this case, however, there is a significant excess of recessives among the ears segregating 15:1, in contrast to a deficiency of about the same magnitude in the preceding cross. Three ears segregating in a ratio of 45:19 indicate that three distinct factors are involved in this cross and that these are independently inherited.

g_{e8} g_{e9} g_{e10}

In a previous paper (MANGELSDORF 1926) the writer recorded the segregation for premature germination on three ears, two of which segregated in a ratio of approximately 8:1, the third in a ratio of 41:1. It was suggested that the 8:1 ratio might be the result of linked duplicate factors with approximately 33.3 percent of crossing over, while the third ear might represent linked duplicate factors in the repulsion phase or a set of triplicate factors, two of which were linked with approximately 33.3 percent crossing over. In addition to making a slight arithmetical error in calculating the ratios that might be expected when F_3 progenies of this ear were grown, I neglected to point out that the possibility of Ear No. 2178 being the result of linked duplicate factors in the repulsion phase was very remote indeed, and that the hypothesis of triplicate factors with linkage between two members of the set was far more plausible. In this case the 8:1 ratios would also presumably be the result of triplicate factors, the independent factor pair being homozygous recessive. Such a combination, in the absence of linkage, should have given 15:1 ratios.

It was realized that such an interpretation could be no more than tentative since any conceivable ratio can be explained by assuming a sufficient number of factors with appropriate degrees of linkage between certain members of the set. If, however, the 8:1 ratios are the result of two linked

factors with crossing over of approximately 33.3 percent, then we should expect to find in F_3 the following types of progenies in the proportion shown:

1. 8 ears segregating 3:1
2. 8 ears segregating 8:1
3. 2 ears segregating 35:1
4. 14 ears not segregating.

Seventeen ears of the F_3 endosperm generation were obtained with the results shown in table 7. Six of these ears were segregating for germinating seeds and it is noted that these ears fall into two distinct groups with regard to the proportion of recessive seeds. All of them deviate by significant amounts from a 3:1 ratio and four deviate significantly from a 15:1 ratio. On the other hand four of the ears fit an 8:1 ratio rather closely and the remaining two approximate a 35:1 ratio fairly well. Both of these ratios should be expected if linked duplicate factors with 33.3 percent crossing over are involved. The 8:1 ratios represent the coupling phase; 35:1 ratios the repulsion phase. Ratios of 3:1, resulting from a homozygous recessive condition of one of the pairs of factors which are also expected in F_3, did not occur. The distribution as a whole, however, is in fairly satisfactory agreement with expectation. In a population of

TABLE 7

F_3 progenies from an ear (Number 2179) segregating in an 8:1 ratio in F_2. Theoretical results calculated on the basis of duplicate factors with 33.3 percent crossing over.

EAR NUMBER	EXPECTED RATIO	NUMBER OF PROGENIES		TOTAL SEEDS	NUMBER GERMINATING	THEORETICAL NUMBER GERMINATING	DEVIATION
		Theoretical	Actual				
	3:1	4.25	0				
3098	8:1			287	25	31.9	−6.9±3.59
3100	"			126	16	14.0	2.0±2.38
3099	"			225	30	25.0	5.0±3.18
3095	"			115	19	12.8	6.2±2.27
Total		4.25	4	753	90	83.6	6.4±5.81
3096	35:1			208	3	5.8	−2.8±1.60
3097	"			51	1	1.4	−.4± .79
Total		1.06	2	259	4	7.2	−3.2±1.78
Not segregating		7.44	11				

seventeen ears the four types of progeny are expected in ratio of 4.25:4.25:1.06:7.44. They are found in the ratio of 0:4:2:11. Applying the formula for goodness of fit we find that $X^2=6.78$ and $P>0.05$.

F_3 progenies from the ear which segregated in a ratio of 41:1 were also grown. If we assume that this ratio is the result of a set of triplicate factors with linkage and 33.3 percent crossing over between two members of the set, then the following types of progenies are expected in F_3:

1. 16 ears segregating 3:1
2. 10 ears segregating 8:1
3. 16 ears segregating 15:1
4. 12 ears segregating 35:1
5. 3 ears segregating 71:1
6. 83 ears not segregating.

Unfortunately the plants grown from this ear were rather weak and only fifteen self-pollinated ears were obtained. Twelve of these did not segregate; the segregation of the remaining three is shown in table 8. With so small a number of segregating ears it is naturally impossible for all the expected types to occur. Yet the agreement with expectancy is fairly close, X^2 being 3.47 and $P>0.5$.

TABLE 8

Segregating F_3 progenies from an ear (Number 2178) segregating in a 41:1 ratio in F_2.

EAR NUMBER	PROBABLE RATIO	TOTAL SEEDS	NUMBER GERMINATING	THEORETICAL NUMBER GERMINATING	DEVIATION
3081	8:1	196	25	21.8	3.2±2.97
3082	15:1	167	10	10.4	− .4±2.11
3080	35:1	141	3	3.9	− .9±1.32
Total		504	38	36.1	1.9±3.90

In lieu of a larger population the best proof that three factors instead of two are involved is the appearance of a progeny segregating in a ratio of 15:1. It would be impossible for such ears to occur if only two linked factors were involved because so long as both factor pairs remained heterozygous only ratios of 8:1 resulting from the coupling phase and ratios of 35:1 resulting from the repulsion phase could occur. If a third factor, not linked with the other two, were involved, however, ratios of 15:1 would be expected in every case that either of the linked factor pairs be-

came homozygous recessive. It may be noted that Ear No. 3082 in table 8 fits a 15:1 ratio very closely. Furthermore, the segregation in this ear deviates from an 8:1 ratio by an amount equal to 3.13 times the error and from a 35:1 ratio by 3.75 times the error. The occurrence of this ear is rather convincing evidence that three factors are involved in this family.

Still another test may be made to determine whether two or three factors are involved in this stock and whether the linked factor hypothesis explains the situation. If a progeny which segregated in a ratio of 8:1 is crossed with an unrelated stock, then the heterozygous hybrid should segregate in a ratio of 8:1 if linked duplicate factors are involved. No ratios other than this could possibly be produced. If three factors are involved, however, and two of these are linked, then only ratios approximately 35:1 could occur in F_2. This ratio is identical with that produced by two factors with the same degree of linkage in the repulsion phase, but by crossing with a totally unrelated stock it is assumed that one of the parents carries none of the recessive factors for premature germination and, hence, the coupling phase is the only one possible.

To make this test an F_4 plant from Ear No. 3081 was crossed by Yellow Creole, a southern variety quite different from the New England stock. Approximately half of the ear was self-pollinated, the other half crossed, the two types of seed being separated by xenia. The segregation among the self-pollinated seeds was 39 dormant:7 germinating; a ratio of 5.6:1. The crossed seeds on the same ear were all dormant. From these, three non-segregating and two segregating ears were obtained in the next generation (F_2 endosperm). The segregation on the latter is shown in table 9. It is noted that the ratios in the two ears are practically alike, 27.5:1 and 28.9:1. Both show a significant deviation from an 8:1 ratio but approach a 35:1 ratio rather closely.

These facts, considered in connection with previous data, furnish rather

TABLE 9

Segregating F_2 progenies from a cross of Ear Number 3081 ($G_{c8}\,g_{c8}\,G_{c9}\,g_{c9}\,G_{c10}\,g_{c10}$) × Yellow Creole ($G_{c8}\,G_{c8}\,G_{c9}\,G_{c9}\,G_{c10}\,G_{c10}$).

EAR NUMBER	PROBABLE RATIO	TOTAL SEEDS	NUMBER GERMINATING	THEORETICAL NUMBER GERMINATING	DEVIATION
5648	35:1	371	13	10.3	2.7±2.13
5649	"	359	12	10.0	2.0±2.10
Total		730	25	20.3	4.7±2.99

convincing evidence that a set of triplicate factors is involved in this stock and that two of these, arbitrarily designated as g_{e8} and g_{e9}, are linked while the third, g_{e10}, is inherited independently of the other two. All must be present, however, in a homozygous recessive condition in order for premature germination to occur.

Although all calculations of theoretical numbers have been based on an assumption of 33.3 percent crossing over between g_{e8} and g_{e9}, a tabulation of all available data would indicate that the percentage is somewhat lower than this and is probably nearer 30 percent.

TABLE 10

Segregating progenies of g_{e11} stock.

EAR NUMBER	GENETIC FACTORS	TOTAL SEEDS	NUMBER GERMINATING	THEORETICAL NUMBER GERMINATING	DEVIATION
3205	g_{e11}	549	158	137.2	20.8±6.8
3206	"	340	85	85.0	.. ..
3207	"	245	71	61.3	9.7±4.6
3208	"	458	112	114.5	−2.5±6.3
3209	"	524	132	131.0	1.0±6.7
Total		2116	558	529.0	29.0±13.4

g_{e11}

No crosses have yet been made with this stock. The character is reported as a distinct type of premature germination because it differs phenotypically in several respects from all other types. As noted in the preliminary description the plumules are pink in color and there is also a pink tinge in the endosperm. In no other types of premature germination has such a condition been found and it seems safe to assume that g_{e11} is genetically distinct from the other types of premature germination, which have been described. The data in table 10 show that this character is inherited as a simple recessive.

G_{e12} g_{e13} g_{e14} g_{e15}

In a study on the inheritance of defective seeds, another type of endosperm character in maize, (MANGELSDORF 1926) it was found that the ratios were subject to slight errors due to the occurrence of non-hereditary defectives of various types on almost every ear. That a similar situation might obtain in the case of premature germination was suggested by the

fact that one or two germinating seeds were occasionally found in ears ordinarily classed as non-segregating. Consequently, all seeds from "non-segregating" ears of the F_2 population were carefully examined with the result that one or more germinating seeds were found on seven ears from the crosses $g_{e1} \times g_{e4}$, $g_{e1} \times g_{e6}\, g_{e7}$ and $g_{e4} \times g_{e6}\, g_{e7}$. The segregation on these ears has already been shown in tables 2, 3, and 6. When the data on these ears are combined as in table 11 it is found that the segregation in three of the ears approaches a 63:1 ratio rather closely, while in the remaining four ears the data do not differ significantly from a ratio of 255:1.

TABLE 11

Ratios of 63:1 and 255:1 from "non-segregating" ears of various crosses.

EAR NUMBER	GENETIC FACTORS	PROBABLE RATIO	TOTAL SEEDS	NUMBER GERMINATING	THEORETICAL NUMBER GERMINATING	DEVIATION
3031	g_{e12} g_{e13} g_{e14}	63:1	90	1	1.4	$-.4 \pm 0.8$
3041	"	"	122	2	1.9	$.1 \pm 0.9$
3042	"	"	219	5	3.4	1.6 ± 1.2
Total			431	8	6.7	1.3 ± 1.7
2952	g_{e12} g_{e13} g_{e14} g_{e15}	255:1	281	1	1.10	$-.10 \pm .71$
2963	"	"	171	1	.67	$.33 \pm .55$
2974	"	"	268	1	1.05	$-.05 \pm .69$
2976	"	"	266	2	1.04	$.96 \pm .69$
Total			986	5	3.85	1.15 ± 1.32

Had only the latter ratios occurred, the matter should probably have been given no further thought. The average number of seeds on the ears of these three crosses is approximately 235, and if one germinating seed occurred as the result of accident or other causes, a ratio approximating 255:1 would be inevitable. The fact, however, that ratios approaching 63:1 also occurred, that all these segregating ears were found in crosses of the same three stocks and that the non-segregating ears from all other crosses were completely free of germinating seeds, suggested with considerable force that genetic factors might be involved in the occasional appearance of these germinating seeds. Paradoxical though it may seem, the fact that the data do not exactly fit 63:1 and 255:1 ratios but show an excess of recessives, may be regarded as additional evidence of genetic segregation in those ratios. With the ears comprising an average total of 235 seeds it would be almost inevitable, as a result of random sampling,

that some of the ears from heterozygous plants should show no recessive seeds. As these ears cannot be identified they are not included as segregating ears and their omission is a constant source of error which tends to raise the proportion of recessives among the ears classed as segregating. How great this error may be in the present case cannot be determined because no record was made of the number of seeds on the non-segregating ears. However, if their average number is the same as that of the segregating ears in the same family, that is, 235, then if one non-segregating, though heterozygous, ear is included the ratio becomes 243:1. If two ears are included the ratio becomes 290:1.

FIGURE 1.—Ears representing some of the ratios which occur in the inheritance of premature germination. From left to right the ratios are 15:1, 3:1, 45:19, 9:7, 135:121 and 27:37. Ears segregating 63:1, 255:1, and 225:31 were also found but were not photographed.

Ears segregating in a ratio of 63:1 are naturally subject to the same error though in a lesser degree. It may be of interest to note, in this connection, that NILSSON-EHLE (1909) in his study of the inheritance of seed coat color in wheat encountered precisely this error in a very marked degree. All of the 384 F_2 plants from a cross between red-seeded and white-seeded parents were red seeded. However, when 78 F_3 progenies were grown, ratios of 63:1, 15:1, and 3:1 were found. The failure of white-seeded plants to occur in F_2 appears to have been merely the result of random sampling, although the odds against the chance occurrence of this combination are approximately 75:1.

F_3 *progenies from various* F_2 *ratios*

In undertaking a study of segregation in F_3, it was obviously impossible, due to limitations of time and space, to grow F_3 progenies from any very large proportion of the F_2 ears, and it was considered more advisable to obtain F_3 progenies of the various ratios encountered in F_2 regardless of the parents involved rather than to grow F_3 progenies from each F_2 ear of any particular cross. In other words it seemed more important to learn, for example, how the F_3 progenies from an ear segregating in a 45:19 ratio in F_2 differed from those segregating 9:7 in F_2, than to attempt to prove that each ear which had been classified as segregating in a 9:7 ratio actually belonged in this category. Consequently, F_3 progenies have been grown from at least one ear representing each of the Mendelian ratios found in F_2 with the exception of the 3:1 ratio. The segregation for premature germination in various ratios is illustrated in figure 1.

Before proceeding with a discussion of the data it should be mentioned that classification in many of the F_3 progenies was subject to an unavoidable error as the result of accidental cross-pollination which inevitably reduces the proportion of recessives. This population came into bloom during a period of rainy weather and as a result many of the bags over the ear shoots were torn and the silks exposed for a brief period to cross-pollination. How great a percentage of cross-pollination occurred is impossible to estimate but the fact that many of the ears bore purple seeds as a result of pollination with other stocks in the vicinity is proof that it did occur. All purple out-crossed seeds were discarded in making the classifications but there were undoubtedly many other out-crossed seeds which could not be identified by color, and which, being classified as dormant, would tend to produce an excess of this class.

9:7 Ratio

Theoretically the dormant seeds from an ear segregating in a ratio of 9:7 should produce the following three types of progenies in the proportions shown:

1. 4 ears segregating 3:1
2. 4 ears segregating 9:7
3. 1 ear not segregating

An ear from the cross of $g_{e1} \times g_{e3}$ shown in table 1 was used to test this hypothesis. The results are shown in table 12. Thirty-five F_3 progenies were obtained. With this number the three types of progenies are expected

TABLE 12

F_3 progenies from Ear Number 2997 (9:7 ratio in F_2) Ge_3 g_{e3} G_{e5} g_{e5}.

EXPECTED RATIOS	NUMBER PROGENIES		TOTAL SEEDS	NUMBER GERMINATING	THEORETICAL NUMBER GERMINATING	DEVIATION
	Theoretical	Actual				
3:1	15.6	21	3295	757	823.8	−66.8±16.8
9:7	15.6	14	2559	1027	1119.6	−92.6±17.0
Not segregating	3.9	0				
Total	35.1	35	5854	1784	1943.4	−159.4±24.3

in a ratio of 15.6:15.6:3.9. They occurred in a ratio of 21:14:0. The agreement with expectancy is reasonably close, X^2 being 5.93 and $P > 0.05$. The recessive seeds in both the 3:1 and 9:7 groups show a marked deficiency which is undoubtedly due to contamination.

27:37 Ratio

Four types of progenies are expected from this ear in the proportions indicated.

1. 6 ears segregating 3:1
2. 12 ears segregating 9:7
3. 8 ears segregating 27:37
4. 1 ear not segregating

TABLE 13

F_3 progenies from Ear Number 2989 (27:37 ratio in F_2) Ge_1 g_{e1} G_{e3} g_{e3} G_{e5} g_{e5}.

EXPECTED RATIOS	NUMBER PROGENIES		TOTAL SEEDS	NUMBER GERMINATING	THEORETICAL NUMBER GERMINATING	DEVIATION
	Theoretical	Actual				
3:1	7.6	9	1549	382	387.3	−5.3±11.5
9:7	15.1	16	2433	1021	1064.4	−43.3±16.5
27:37	10.1	7	1221	659	705.9	−46.9±11.6
Not segregating	1.3	2				
Total	34.1	34	5203	2062	2157.6	−95.6±24.0

Thirty-four progenies were obtained from Ear No. 2989, which had segregated in a ratio of 27:37 and was presumably heterozygous for g_{e1}, g_{e3}, and g_{e5}. With a population of this size the four types of progeny are expected in the ratio of 7.6:15.1:10.1:1.3. As shown in table 13, they oc-

curred in the ratio of 9:16:7:2. The results are in close agreement with expectancy, X^2 being 1.64 and $P > 0.50$.

15:1 Ratio

Progenies from plants segregating in a ratio of 15:1 should fall into three groups in the following proportions:

1. 4 ears segregating 3:1.
2. 4 ears segregating 15:1
3. 7 ears not segregating.

TABLE 14

F_3 progenies from Ear Number 3048 (15:1 ratio in F_2) G_{c6} g_{c6} G_{c7} g_{c7}.

EXPECTED RATIOS	NUMBER PROGENIES		TOTAL SEEDS	NUMBER GERMINATING	THEORETICAL NUMBER GERMINATING	DEVIATION
	Theoretical	Actual				
3:1	8.5	7	1605	326	401.3	−75.3±11.7
15:1	8.5	6	1188	40	74.2	−34.2± 5.7
Not segregating	14.9	19				
Total	31.9	32	2793	366	475.5	−109.5±13.4

Thirty-two progenies were grown with the results shown in table 14. The theoretical distribution of 32 ears among these three groups is 8.5: 8.5:14.9. The actual distribution is 7:6:19. The two distributions are in close agreement, X^2 being 2.14 and $P > 0.30$. In this case as in those already presented there is a deficiency of recessive seeds in both classes of segregating progeny, probably due to cross-pollination.

45:19 Ratio

A ratio of 45:19 is presumably the product of 3:1 and 15:1 ratios; one pair of complementary and a set of duplicate factors being involved. Consequently, five types of progenies are expected in F_3 in the following proportions:

1. 18 ears segregating 3:1
2. 4 ears segregating 15:1
3. 8 ears segregating 45:19
4. 8 ears segregating 9:7
5. 7 ears not segregating.

The 9:7 ratios are expected from plants that are heterozygous for the complementary factor and heterozygous for one pair of duplicate factors but homozygous recessive for the other pair.

TABLE 15

F_3 progenies from Ear Number 3033 (45:19 ratio in F_2) $G_{c1}\,g_{c1}\,G_{c8}\,g_{c8}\,G_{c7}\,g_{c7}$.

EXPECTED RATIOS	NUMBER PROGENIES		TOTAL SEEDS	NUMBER GERMINATING	THEORETICAL NUMBER GERMINATING	DEVIATION
	Theoretical	Actual				
3:1	14.4	11	1989	480	497.3	−17.3±13.1
15:1	3.2	5	722	50	45.1	4.9± 4.4
45:19	6.4	5	652	198	193.6	4.4± 7.9
9:7	6.4	7	1049	440	458.9	−18.9±10.9
Not segregating	5.6	8				
Total	36.0	36	4412	1168	1194.9	−26.9±19.9

Thirty-six F_3 progenies were obtained with the results set forth in table 15. With a population of this size the five types of progeny are expected in a ratio of 14.4:3.2:6.4:6.4:5.6. They occurred in a ratio of 11.5:5:7:8. The agreement with expectation is very close, X^2 being 3.21 and $P > 0.50$. In this case the segregation within each group is also very close to expectation, there being no significant deviations.

135:121 Ratio

This ratio is presumably the product of 9:7 and 15:1 ratios. If this is true, four factor pairs are involved; two pairs of complementary factors and a set of duplicate factors. Seven classes of F_3 progenies are expected in the following proportions:

1. 32 ears segregating 3:1
2. 44 ears segregating 9:7
3. 16 ears segregating 27:37
4. 4 ears segregating 15:1
5. 16 ears segregating 45:19
6. 16 ears segregating 135:121
7. 7 ears not segregating.

Table 16 shows that with a population of 46 ears all the expected types of progenies, with the exception of those segregating in a ratio of 27:37, have occurred. With a population of this size the seven types are expected in a ratio of 10.9:15.0:5.5:1.4:5.5:5.5:2.4. They occurred in a ratio of 21:7:0:4:10:2:2. This array differs significantly from the theoretical,

X^2 being 34.31 and $P < 0.01$. The segregation within each class, however, is in very close agreement with expectancy in every case.

TABLE 16

F_3 progenies from Ear Number 2947 (135:121 ratio in F_2) G_{c1} g_{c1} G_{c2} g_{c2} G_{c6} g_{c6} G_{c7} g_{c7}.

EXPECTED RATIOS	NUMBER PROGENIES		TOTAL SEEDS	NUMBER GERMINATING	THEORETICAL NUMBER GERMINATING	DEVIATION
	Theoretical	Actual				
3:1	10.9	21	3911	970	977.8	−7.8±18.2
9:7	15.0	7	1087	459	475.5	−16.5±11.0
27:37	5.5	0				
15:1	1.4	4	903	56	56.4	−0.4± 4.9
45:19	5.5	10	1926	595	571.8	23.2±13.5
135:121	5.5	2	456	225	215.5	9.5± 7.2
Not segregating	2.4	2				
Total	46.2	46	8283	2305	2297.0	5.0±27.5

Since a ratio of 135:121 seldom differs significantly from a 9:7 ratio, probably the best proof that the parent ear of these progenies segregated in the former ratio and not the latter is the appearance of 15:1 ratios in F_3. It would be impossible, as the result of recombination, for such a ratio to appear in the progenies of an ear segregating 9:7. The same holds true for the 45:19 ratios. The fact that both of these have appeared in F_3 is ample evidence that the F_2 ratio could not have been 9:7 in spite of the fact that the seven types of progeny have not appeared in the proportions expected from a ratio of 135:121.

63:1 and 255:1 Ratios

Ratios of 255:1 are presumably the result of a set of quadruplicate factors, all four factor pairs being heterozygous. The 63 :1 ratios are assumed to be due to the same factor complex except that one of the four factor pairs is homozygous recessive. The latter should produce four types of progenies in the following proportions:

1. 6 ears segregating 3:1
2. 12 ears segregating 15:1
3. 8 ears segregating 63:1
4. 37 ears not segregating.

Twenty-eight F_3 progenies were obtained with the results shown in table 17. With a population of this size the four classes are expected in a ratio of 2.7:5.3:3.6:16.4. They occurred in the proportion of 0:2:3:23. Although no ears segregating in a ratio of 3:1 were obtained, the observed

array as a whole shows a reasonably close agreement with the theoretical array, X^2 being 7.52 and $P > 0.05$. The segregation within each class is also in agreement with expectation, the deviations being less than three times the error in both types of segregating progenies.

TABLE 17

F_3 progenies of Ear Number 3041 (63:1 ratios) G_{e12} g_{e12} G_{e13} g_{e13} G_{e14} g_{e14} G_{e15} g_{e15}.

EXPECTED RATIOS	NUMBER PROGENIES		TOTAL SEEDS	NUMBER GERMINATING	THEORETICAL NUMBER GERMINATING	DEVIATION
	Theoretical	Actual				
3:1	2.7	0				
15:1	5.3	2	431	18	26.9	-8.9 ± 3.39
63:1	3.6	3	505	7	7.9	$-.9 \pm 1.88$
Not segregating	16.4	23				
Total	28.0	28	936	25	34.8	-9.8 ± 3.92

From an ear segregating 255:1, the following F_3 progenies are expected:

1. 8 ears segregating 3:1
2. 24 ears segregating 15:1
3. 32 ears segregating 63:1
4. 16 ears segregating 255:1
5. 175 ears not segregating.

TABLE 18

F_3 progenies of Ears Numbers 2974 and 2952 (255:1 ratio) G_{e12} g_{e12} G_{e13} g_{e13} G_{e14} g_{e14} G_{e15} g_{e15}.

EXPECTED RATIOS	NUMBER PROGENIES		TOTAL SEEDS	NUMBER GERMINATING	THEORETICAL NUMBER GERMINATING	DEVIATION
	Theoretical	Actual				
3:1	2.3	1	216	23	54.0	-31.0 ± 4.29
15:1	7.0	4	482	28	30.1	-2.1 ± 3.58
63:1	9.3	6	1224	11	19.1	-8.1 ± 2.93
255:1	4.6	4	1005	4	3.9	0.1 ± 1.33
Not segregating	50.8	59				
Total	74.0	74	2927	66	107.1	-41.1 ± 6.86

F_3 progenies from two F_2 ears were grown and 74 self-pollinated ears were obtained. With this population the five classes are expected in the ratio of 2.3:7.0:9.3:4.6:50.8. Table 18 shows that they occurred in the proportions of 1:4:6:4:59. The agreement is reasonably close, X^2 being 4.60 and $P > 0.30$. It is noted, however, that the segregation within the

classes is not particularly close to expectation. The progenies segregating 3:1 and 15:1 both show a significant deficiency of recessive seeds. Progenies segregating in a 63:1 ratio also show a slight deficiency, while those segregating 255:1 are almost in perfect agreement with the theoretical ratio. In the latter case a slight excess of recessives would be expected, as has previously been pointed out, due to the exclusion of ears, which though heterozygous for all four factors pairs, produce no germinating seeds as the result of the operations of random sampling.

These consistent deficiencies of recessives in all four classes of segregating ears are probably due to contamination. Purple outcrossed seeds were particularly numerous in these progenies and other out-crossed seeds which could not be identified by color were probably just as numerous, or more so, as stocks with purple aleurone were further removed than other unrelated stocks with colorless aleurone.

In spite of this unfortunate error the evidence supporting a four factor hypothesis seems to be rather convincing. A consideration of the combined results of F_2 and F_3 leaves little doubt that the premature germination on these ears is inherited and that at least four recessive factors in a homozygous condition are necessary for premature germination to occur.

Although no crosses have been made between this stock and others which segregate for germinating seeds, it is not difficult to demonstrate that a different set of genetic factors is probably involved. It is fairly certain that the character is distinct from g_{e1}, g_{e2}, g_{e3}, g_{e4}, g_{e5}, and g_{e11} and because the latter are in each case governed by a single pair of complementary factors. The character is undoubtedly distinct from g_{e8} g_{e9} g_{e10} because in this set of triplicate factors two of the genes are apparently linked while the data on g_{e12} g_{e13} g_{e14} g_{e15} indicate independent inheritance. Finally, this character is probably distinct from that produced by the duplicate factors g_{e6} g_{e7} because several ears of the latter have been found which were also segregating for g_{e12} g_{e13} g_{e14} g_{e15}. When these two types occurred on the same ear they could be readily separated, as the former produced a well developed plumule, while the latter showed only a slight elongation of the plumule beyond the region of the germ. To give but one example of the segregation of both types in the same ear, an F_3 progeny from Ear No. 2947 bore 273 dormant seeds, 22 seeds of the g_{e12-15} type and 26 seeds of the g_{e6-7} type. Apparently both types were segregating in a ratio of 15:1 so that the complete ratio would be 225:15:16. With a population of 321 seeds the theoretical distribution is 282:19:20. This agrees fairly well with the observed results, X_2 being 2.55 and $P > 0.20$.

Summary of segregation

Table 19 brings together in compact form practically all of the available data from each type of Mendelian ratio that has appeared in these studies. In making up this summary the data from tables 12 and 14 have been omitted because every class of segregating progeny included in these two tables shows a marked deficiency of recessives that cannot be attributed to chance and is undoubtedly due to accidental cross-pollination.

With the exception of the 9:7 and 45:19 ratios the data are in close agreement with expectation. No cause is known for the significant deficiency of recessives in the former and significant excess in the latter, although in the case of the 9:7 ratios part of the deficiency may be partly accounted for by cross-pollination.

TABLE 19

Summary of segregation classified according to Mendelian ratios.

FACTOR COMBINATIONS	THEORETICAL RATIOS	TOTAL SEEDS	NUMBER GERMINATING	THEORETICAL NUMBER GERMINATING	DEVIATION	DEV. / P.E.
1 pair complementary	3:1	20430	5074	5108	−34±41.7	.8
2 pairs complementary	9:7	10521	4420	4603	−183±34.3	5.3
3 pairs complementary	27:37	2545	1444	1471	−27±16.8	1.6
1 set duplicate	15:1	7873	491	492	−1±14.5	.1
1 set triplicate	63:1	2160	26	34	−8± 3.9	2.0
1 set quadruplicate	255:1	1991	9	8	1± 1.9	.5
1 set duplicate: 1 pair complementary	45:19	5008	1569	1487	82±21.8	3.8
1 set duplicate: 2 pairs complementary	135:121	689	339	326	13± 8.8	1.5
Totals		51217	13372	13529	−157±67.3	2.3

Considering the population of 51,217 seeds as a whole, it is found that the total number of germinating seeds does not differ significantly from the theoretical number determined by totalling the calculated numbers for each class. The deviation is -157 ± 67.3.

The percentage of recessives in this population has varied from 0.39 percent in the 255:1 ratios to 57.81 percent in the 27:37 ratios, with intervening values ranging between these two extremes. The situation would have been hopelessly confusing had all these varying percentages appeared in a single population but occurring as they did in unrelated stocks, their analysis proved to be relatively simple.

These data furnish an excellent example of the tremendous complexity that may be expected from simple Mendelian combinations behaving in an orthodox fashion. When the disturbing effects of linkage and differential pollen-tube growth are also considered, it is evident that almost any percentage of recessives from 0–100 might occur. Even without these disturbing influences it is theoretically possible with the factors already studied to obtain a combination showing 92.49 percent of germinating seeds.

NUMBER OF DISTINCT FORMS OF PREMATURE GERMINATION.

The fifteen genetic factors for premature germination represent nine different types of premature germination. The evidence, though not complete, is sufficient to indicate that all of these are genetically distinct. That g_{c1}, g_{c3} and g_{c5} are genetically different is shown by the 27:37 ratios which are found when all three types occur in the same progeny. The marked phenotypical differences between g_{c4} and the types just mentioned are almost sufficient to prove that g_{c4} is different from the remaining three. In addition crosses of g_{c4} with g_{c1} and g_{c3} show the former to be genetically unlike the latter. The genotype g_{c2} has been crossed only with g_{c1} (MANGELSDORF 1926). Since the germination in g_{c2} is not always clear cut, this stock has been discarded, and the only evidence that it is different from the other stocks is of a morphological nature. This is also true of g_{c11}.

Because of the difference in mode of inheritance, it is almost certain that the genotype g_{c6} g_{c7} differs genetically from the five genotypes in which only one factor pair is involved. Crosses of g_{c6} g_{c7} with g_{c1}, g_{c3} and g_{c4} bear out this assumption, ratios of 45:19 having been observed in every case.

The genotype g_{c8} g_{c9} g_{c10} has not been tested in crosses. It is undoubtedly different from genotypes g_{c1}–g_{c5} because of the different mode of inheritance. Linkage of two members of this set of triplicate factors indicates that this genotype differs from g_{c6} g_{c7} and from g_{c12} g_{c13} g_{c14} g_{c15}, although there is a possibility that either, or both, of the latter may be homozygous recessive for an additional factor, which, if brought to light, would display linkage with one of those already known. This possibility is remote in the case g_{c6} g_{c7} as this character has been crossed with a number of unrelated stocks and no indication of additional factors has been found. The genotype g_{c12} g_{c13} g_{c14} g_{c15} has been shown to be distinct from g_{c6} g_{c7} by the segregation of both characters on the same ear. We may consider it, tentatively at least, to be different from g_{c8} g_{c9} g_{c10} because the latter exhibits linkage, the former not. The discovery of additional factors, however, in

either set might possibly show the two characters to be the result of the same factor combination.

With the exception of g_{e2}, and perhaps g_{e11}, the evidence is fairly conclusive in showing nine distinct types of premature germination, involving 15 genetic factors, to have occurred in the course of these studies.

DISCUSSION

The inheritance of premature germination is but another demonstration of the large number of genetic factors involved in a relatively simple phenomenon. Dormancy of the seed during development is so general that it may almost be taken for granted. Yet we find that at least fifteen different genetic factors are involved in maintaining dormancy and we can scarcely suppose that this is more than a sample of the total number.

As has been the case in several other characters in maize, two types of inheritance involving complementary and multiple factors, respectively, have been encountered. It is a temptation to assume that these two types of genetic phenomena are associated with distinct types of physiological reactions involved in maintaining dormancy. We might postulate, for example, that a series of complementary factors governs the formation of a group of substances, enzymes or inhibitors, all of which must be present in order to maintain dormancy, while a series of duplicate factors is responsible for another group of substances any of which will inhibit germination. In the first case the seed will germinate prematurely whenever any one of the essential inhibitors is lacking; in the latter case it will germinate only when all are lacking.

There is, at present, no evidence in support of such an interpretation. It may be more than a coincidence, however, that all the types of premature germination in which complementary factors are involved, occur relatively early in the development of the seed, while those in which multiple factors are involved occur relatively late. There are six characters in the former category and three in the latter. The test for independence shows the odds against the chance occurrence of this combination to be large, P being considerably less than 0.01. Perhaps these odds should not be taken too seriously as only nine characters are being considered and there is no sharp distinction between "early" and "late."

Since the discovery of duplicate factors and the introduction of the multiple factor hypothesis which was formulated independently by NILSSON-EHLE (1908) and EAST (1910), many cases of inheritance which fall into the category of duplicate factors have been recorded and there has

been no small amount of speculation regarding the origin of this hereditary mechanism.

The attractive, and very plausible, hypothesis of the origin of duplicate factors through doubling of the original chromosomes has met with several objections, two of which have been discussed in some detail by SHULL (1926). The first is that only certain characters exhibit the type of inheritance expected from duplicate factors, while other characters in the same race and even in the same linkage group are inherited as simple recessives. The second objection is that a doubling of the chromosomes would be expected to result, as MULLER (1914) pointed out some years ago, in ratios of 35:1 if the four homologous chromosomes assort at random. Ratios of 15:1 would not be obtained unless the four chromosomes should assort as two independent disomes rather than as a single tetrasome. SHULL (1926) states that deviations from a 15:1 ratio and approaching the tetrasomic ratio of 35:1 have occasionally been encountered in Bursa. In maize, DEMEREC (1923), working with albino seedlings, and the writer, in studies of premature germination, have observed ratios approaching 35:1. These have, however, been assumed to be the result of linkage of duplicate factors (repulsion phase) or linkage of two members of a set of triplicate factors. My own data from several generations fit the latter interpretation very well indeed, but there is always the possibility that additional studies will throw an entirely new light on the situation.

Probably a more serious objection to the chromosome duplication theory, at least as it applies to maize, is the occurrence of triplicate and quadruplicate factors. While these can be explained, as are duplicate factors involving two factor pairs, by additional doubling of the chromosomes, there is an arithmetical limit to the number of duplications which could have occurred to produce the present ten pairs. On the other hand it is by no means certain we have found the limit in the number of factors involved in the expression of a single simple character such as premature germination, although it is admittedly difficult to discover combinations larger than four factor pairs in population of the size ordinarily produced by single plants of maize.

If multiple factors have arisen through chromosome duplication, then the character g_{s12-15} which is the expression of four independent factor pairs accounts for four chromosomes, in the present complement of ten, which have originated from a single chromosome during the course of evolution of maize. If this were the case, perhaps we might expect that four of the present chromosomes would show considerable morphological

resemblance. A recent paper by McCLINTOCK (1929) indicates that this is not the case. Miss McCLINTOCK is convinced that every chromosome in maize is morphologically identifiable, differing from every other in some essential feature.

It is possible that the hypothetical transition from tetrasomic to disomic inheritance, that is, from a tetraploid to a "double diploid," has been accompanied by discernible morphological changes in chromosomes that were originally identical and homologous. The fact remains, however, that at present there is very little, if any, critical evidence that multiple factors arise through chromosome duplications. The hypothesis remains a plausible one, however, particularly in view of the fact that duplicate factors and polyploidy are both of frequent occurrence in plants and of rare occurrence in animals.

SIRKS (1926) suggests that some cases of inheritance attributed to duplicate factors are interpreted equally well by the molecular hypothesis of CORRENS (1919) which postulates that molecules in homologous chromosomes can exchange in either direction one or more of the atoms of which they are constituted. Thus, what appears to be a series of multiple factors might in reality be a series of multiple allelomorphs. SIRKS' argument was partly based on the assumption that it had never been shown conclusively that certain Mendelian factors were linked with one of several members of a series of multiple factors and inherited independently of other members of the series. He was not familiar at that time, however, with the work of WARREN (1924) on inheritance of egg size in Drosophila and LINDSTROM (1926) on the inheritance of size of fruit in the tomato. Both of these writers have definitely localized in certain linkage groups one or more of the genes of a series of multiple factors.

In view of these facts, SIRKS' argument loses much of its force. We must not overlook the possibility, however, of a more complex situation than simple re-combination of duplicate factors, particularly when the data show marked deviations from normal ratios, and appear, at first glance, to suggest linkage. Perhaps it is more than a coincidence that the ratios 8:1 and 27:1, which DEMEREC (1923) found in the case of white seedlings; the ratio of 10:1 which STEWART (1928) encountered in a study of inheritance of awns in several crosses of wheat; and the ratios of 7.5:1 and 35:1 in premature germination which I have recorded in this paper, are so closely alike. All have been interpreted on the basis of duplicate factors with linkage and crossing over of the order of 33 percent. This appears to be the most simple interpretation and is probably justified until more adequate linkage tests with other factors of the same linkage group, or data of another nature, show that it is no longer tenable.

SUMMARY

1. Premature germination is an inherited character in which the seeds fail to maintain dormancy during development and germinate before maturity.

2. This character has appeared in many different stocks of maize, in several cases when two stocks were crossed, and in others in the second and third generation of inbreeding.

3. At least fifteen different genetic factors and nine distinct characters are shown to be involved in the inheritance of premature germination. There are recognizable differences between some of the types in the time at which germination begins as well as in other phenotypical characteristics.

4. Six of the characters are the result of complementary factors and are inherited in ratios of 3:1, 9:7, and 27:37, depending on the number of factors involved in the cross.

5. Three characters are governed by duplicate, triplicate, or quadruplicate factors and are inherited in ratios of 15:1, 63:1, and 255:1.

6. Ratios of 8:1 and 35:1 are interpreted as a result of triplicate factors, two of which are linked with approximately 33 percent of crossing over.

7. Combinations of 3:1 and 15:1 ratios produce a ratio of 45:19. Combinations of 9:7 and 15:1 ratios result in a ratio of 135:121.

8. Practically all of the different Mendelian ratios encountered have been verified by the data from F_3 progenies.

9. The possible origin of duplicate factors through chromosome doubling is discussed in detail.

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